(19) DANMARK

(10) DK/EP 2785693 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 211/86 (2006.01)* *A 61 K 31/4418 (2006.01)* *A 61 K 31/4427 (2006.01)*
A 61 P 3/00 (2006.01) *C 07 D 211/90 (2006.01)* *C 07 D 401/04 (2006.01)*
C 07 D 401/10 (2006.01) *C 07 D 401/12 (2006.01)* *C 07 D 401/14 (2006.01)*
C 07 D 407/14 (2006.01) *C 07 D 413/04 (2006.01)* *C 07 D 413/12 (2006.01)*
C 07 D 417/04 (2006.01) *C 07 D 417/14 (2006.01)* *C 07 F 9/40 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2016-09-05**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-05-18**

(86) Europæisk ansøgning nr.: **12821212.3**

(86) Europæisk indleveringsdag: **2012-11-30**

(87) Den europæiske ansøgnings publiceringsdag: **2014-10-08**

(86) International ansøgning nr.: **US2012067173**

(87) Internationalt publikationsnr.: **WO2013082345**

(30) Prioritet: **2011-12-02 US 201161566039 P** **2012-11-29 US 201213688584**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Bristol-Myers Squibb Company, Route 206 and Province Line Road, Princeton, NJ 08543, USA**

(72) Opfinder: **TURDI, Huji, c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, USA**
HANGELAND, Jon J., c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, USA
LAWRENCE, R. Michael, c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, USA
CHENG, Dong, c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, USA
AHMAD, Saleem, C/o Bristol-Myers Squibb Company, Route 206&Province Line Road, Princeton, New Jersey 08543, USA
MENG, Wei, c/o Bristol-Myers Squibb Company`, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, USA
BRIGANCE, Robert Paul, c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, USA
DEVASTHALE, Pratik, c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, USA
ZHAO, Guohua, c/o Bristol-Myers Squibb Company, 311 Pennington-Rocky Hill Road, Pennington, New Jersey, USA

(74) Fuldmægtig i Danmark: **Marks & Clerk (Luxembourg) LLP, 44 rue de la Vallée, B.P. 1775, L-1017 Luxembourg, Luxembourg**

Fortsættes ...

(54) Benævnelse: **ARYLDIHYDROPYRIDONER OG PIPERIDONER SOM MGA2-INHIBITORER**

(56) Fremdragne publikationer:
WO-A1-2010/095767
US-A1- 2010 093 771
NAGAI: NIPPON KAGAKU ZASSHI, vol. 89, 1968, pages 819-820, XP002693199, ISSN: 0369-5387
AKIO SAKURAI ET AL: "The Cyclization of Ethyl Cyanoacetate and Ketones by Ammonium Acetate", BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 40, no. 7, 1 January 1967 (1967-01-01), pages 1680-1684, XP055055179, ISSN: 0009-2673, DOI: 10.1246/bcsj.40.1680
S. M. MCELVAIN ET AL: JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 80, no. 15, 5 August 1958 (1958-08-05), pages 3915-3923, XP055055161, ISSN: 0002-7863, DOI: 10.1021/ja01548a030
ATTIA A ET AL: "Synthesis of some 3-cyano-5,6-dihydropyridin-2-ones and their N-substituted derivatives", EGYPTIAN JOURNAL OF CHEMISTRY, THE EGYPTIAN CHEMICAL SOCIETY, CAIRO, vol. 26, no. 5, 1 January 1983 (1983-01-01), pages 447-452, XP009167683, ISSN: 0367-0422
CARRIE: "SUR LA CONDENSATION DE LA BENZALACETOPHENONE ET DE LA DYPNONE AVEC LA CYANACETAMIDE", COMPTES RENDUS HEBDOMADAIRES DES SEANCES DE L'ACADEMIE DES SCIENCES, vol. 257, no. 18, 1963, pages 2849-2851, XP009167680, ISSN: 0001-4036

DESCRIPTION

FIELD OF THE INVENTION

[0001] The present invention provides novel aryl dihydropyridinone and piperidinone compounds, and their analogues thereof, which are MGAT2 inhibitors, compositions containing them, and such compounds and compositions for use in therapy, for example, for use in the treatment or prophylaxis of diabetes, obesity, dyslipidemia and related conditions.

BACKGROUND OF THE INVENTION

[0002] The prevalence of obesity and diabetes is increasing at an alarming rate. According to WHO, in 2008, 70% of the U.S. adult population was overweight, and among them 33% were obese. Parallel to the explosive number of people becoming overweight and obese, in 2008, it was estimated that 12.3% of the U.S. population had elevated blood glucose [http://www.who.int/diabetes/facts/en/]. The obesity/diabetes epidemic is not unique to the U.S. According to WHO (Fact Sheet No. 312, September 2012), 347 million people worldwide have diabetes. Treating obesity and improving glycemic control effectively and safely remain major challenges for modem medicine.

[0003] Monoacylglycerol acyltransferase 2 (MGAT2) has emerged as an attractive target for the treatment of obesity and type II diabetes [Yen, C.L. et al., Nat. Med., 15(4):442-446 (2009)]. MGAT2 is highly and selectively expressed in the small intestine where it exerts a pivotal role in the monoacylglycerol-pathway for the absorption of dietary fat. When dietary fat is ingested, pancreatic lipase digests triglycerides into free fatty acids and 2-monoacylglycerol, which are absorbed by intestinal epithelial enterocytes. Once inside enterocytes, free fatty acids and 2-monoacylglycerol are used as building blocks to resynthesize triglycerides by two sequential acylation steps; first by MGAT and then by DGAT enzyme reactions. Triglycerides are then incorporated into chylomicrons and secreted into lymph to be utilized as an energy supply for the body. MGAT2 knockout mice exhibit a healthy metabolic phenotype and show resistance to high-fat diet induced obesity, improvement in insulin sensitivity and decreased fat accumulation in liver and adipose tissue. In addition, genetic deletion of MGAT2 produces mice with increased levels of GLP1 [Yen, C.L. et al., Nat. Med., 15(4):442-446 (2009)]. Taken together, these data show that MGAT2 inhibitors hold promise to treat metabolic disorders such as obesity, type II diabetes and dyslipidemia.

[0004] WO 2010/095767 discloses pyrimidin-4(3H)-one derivatives that inhibit MGAT2 activity and which are useful agents for treating and/or preventing hyperlipiderma, diabetes and obesity.

[0005] US2010/093771 discloses bicyclic pyrimidine compounds that inhibit MGAT activity.

SUMMARY OF THE INVENTION

[0006] The present invention provides aryl dihydropyridinone and piperidinone compounds, and their analogues thereof, which are useful as MGAT2 inhibitors, including stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

[0007] The present invention also provides processes and intermediates for making the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

[0008] The present invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or stereoisomers, tautomers, pharmaceutically acceptable salts, or solvates thereof.

[0009] The compounds of the invention may be used in the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2, such as diabetes, obesity, dyslipidemia and related conditions, such as microvascular and macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, disorders of glucose and lipid metabolism and other maladies.

[0010] The compounds of the invention may be used in therapy.

[0011] The compounds of the invention may be used for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

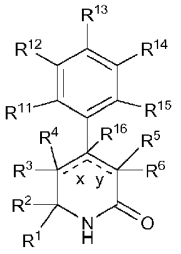
[0012] The compounds of the invention can be used alone, in combination with other compounds of the present invention, or in combination with one or more other agent(s).

[0013] Other features and advantages of the invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

I. COMPOUNDS OF THE INVENTION

[0014] In a first aspect, the present invention provides, *inter alia,* a compound of Formula (I):



(I)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, wherein:

designates a single or double bond;

x and y can be both a single bond; when x is a double bond, then y is a single bond and R^4 and R^{16} are absent; when y is a double bond, then x is a single bond and R^5 and R^{16} are absent;

R^1 is independently selected from the group consisting of: -CONH(C_{4-18} alkyl), -CONHC_{2-8} haloalkyl, -CONH$(CH_2)_{1-8}$Ph, -CONHCH_2COC_{2-8} alkyl, -$(CH_2)_m$-(C_{3-10} carbocycle substituted with 0-2 R^b and 0-2 R^g), -$(CH_2)_m$-(5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g), and a C_{1-12} hydrocarbon chain substituted with 0-3 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated;

R^2 is independently selected from the group consisting of: C_{1-4} alkyl, C_{3-4} cycloalkyl, and C_{1-4} haloalkyl;

R^3 is independently selected from the group consisting of: H, F, Cl, C_{1-4} alkyl and CN;

R^4 and R^5 are independently selected from the group consisting of: H, F, Cl, and C_{1-4} alkyl;

when x is a single bond, R^3 and R^4 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^6 is independently selected from the group consisting of: H, halo, C_{1-4} alkyl, NO_2, R^c, -$(CH_2)_n$-$(X)_t$-$(CH_2)_m R^c$, NH_2, -CONH(C_{1-6} alkyl), -NHCO$X_1SO_2R^j$, -NHCO$CH_2PO(OEt)_2$, -NHCOCOR^j, -NHCOCH(OH)R^j, -NHCOCH_2COR^j, -NHCONHR^j, and -OCONR^fR^j;

X is independently selected from the group consisting of: O, S, NH, CONH, and NHCO;

X_1 is independently C_{1-4} hydrocarbon chain optionally substituted with C_{1-4} alkyl or C_{3-4} cycloalkyl;

when y is a single bond, R^5 and R^6 may be combined with the carbon atom to which they are attached to form a 3- to 6-membered carbocycle;

R^{11}, R^{12}, R^{13}, R^{14} and R^{15} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-2 R^i, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, -$(CH_2)_m$-C_{3-6} cycloalkyl, CN, NR^fR^j, OR^j, SR^j, $NHCO_2$(C_{1-4} alkyl), $NHSO_2$(C_{1-4} alkyl),

and a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S;
alternatively, R^{11} and R^{12}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;
alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;

R^{16} is independently selected from the group consisting of: H and C_{1-4} alkyl;

R^a is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $N(C_{1-4}$ alkyl$)_2$, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, and $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^b is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-10} haloalkyl, C_{1-10} haloalkoxy, C_{1-10} alkylthio, C_{1-10} haloalkyltho, $N(C_{1-4}$alkyl$)_2$, $-CONH(CH_2)_{4-20}H$, $-O(CH_2)_sO(C_{1-6}$ alkyl), R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, and $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$

R^c is, at each occurrence, independently selected from the group consisting of: C_{3-6} cycloalkyl substituted with 0-2 R^d, C_{3-6} cycloalkenyl substituted with 0-2 R^d, $-(CH_2)_m-$(phenyl substituted with 0-3 R^d), and a 5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^d;

R^d is, at each occurrence, independently selected from the group consisting of: halo, OH, CN, NO_2, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl, OBn and phenyl substituted with 0-2 R^h;

R^e is, at each occurrence, independently selected from the group consisting of: H, C_{1-8} alkyl, C_{1-8} haloalkyl, benzyl optionally substituted with C_{1-4} alkoxy, $CO(C_{1-4}$ alkyl) and COBn;

R^f is, at each occurrence, independently selected from the group consisting of: H and C_{1-4} alkyl;

R^g, R^h and R^i are, at each occurrence, independently selected from the group consisting of: halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

R^j is, at each occurrence, independently selected from the group consisting of: C_{1-4} alkyl, C_{3-4} cycloalkyl and phenyl;

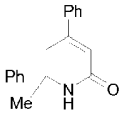
n, at each occurrence, is independently 0 or 1;

m, at each occurrence, is independently 0, 1, 2, 3, or 4;

s, at each occurrence, is independently 1, 2, or 3; and

t, at each occurrence, is independently 0 or 1;

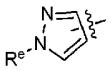
provided that the following compound is excluded:



[0015] In a second aspect, the present invention includes a compound of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the first aspect, wherein:

R^1 is independently selected from the group consisting of: $-CONHC_{4-18}$ alkyl, $-CONH(CH_2)_{1-8}$ Ph, C_{1-12} alkyl substituted with 0-2 R^a, C_{1-12} alkenyl substituted with 0-2 R^a, C_{1-12} alkynyl substituted with 0-2 R^a, $-(CH_2)_m-$(phenyl substituted with 0-1 R^b and 0-2 R^g), $-(CH_2)_m-(C_{3-6}$ cycloalkyl substituted with 0-1 R^b), and $-(CH_2)_m-$(5- to 6-membered heteroaryl substituted with 0-1 R^b and 0-2

R^g), wherein said heteroaryl is selected from: pyridyl, oxazolyl, thiazolyl and



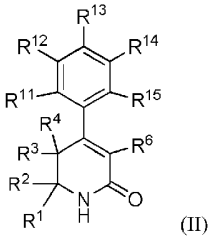
[0016] In a third aspect, the present invention includes a compound of Formula (I), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the first or second aspect, wherein:

R^{11} and R^{15} are independently selected from the group consisting of: H, C_{1-4} alkyl and halo;

R^{12} and R^{14} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy; and

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 R^1, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m$-C_{3-4} cycloalkyl, CN, NR^fR^j, SR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), and a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N,NR^e,O, and S.

[0017] In a fourth aspect, the present invention provides a compound of Formula (II):

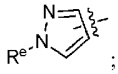


(II)

or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof; within the scope of any of the above aspects.

[0018] In a fifth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the above aspects, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl, C_{3-6} cycloalkyl, $-CONHC_{4-18}$ alkyl, $-CONHC_{2-8}$ haloalkyl, $-CONH(CH_2)_{1-8}$ Ph, $-(CH_2)_m$-(phenyl substituted with 1 R^b and 0-2 R^g), and a 5- to 6-membered heteroaryl substituted with 0-1 R^b and 0-2 R^g, wherein said heteroaryl is selected from: pyridyl, oxazolyl, thiazolyl and



;

R^2 is independently selected from the group consisting of: C_{1-4} alkyl and C_{1-4}haloalkyl;

R^3 is independently selected from the group consisting of: H and F;

R^4 is independently selected from the group consisting of: H and F;

R^6 is independently selected from the group consisting of: NH_2, $-CONH(C_{1-6}$ alkyl), R^c, $-(CH_2)n-(X)_t-(CH_2)_mR^c$, $-NHCO(CH_2)SO_2(C_{1-4}$alkyl), $-NHCOCH_2PO(OEt)_2$, $-NHCOCO(C_{1-4}$ alkyl), $-NHCOCH(OH)(C_{1-4}$ alkyl), $-NHCOCH_2CO(C_{1-4}$ alkyl), $-NHCONH(C_{1-4}$ alkyl), and $-OCONH(C_{1-4}$ alkyl);

R^{11} and R^{15} are independently selected from the group consisting of: H, C_{1-4} alkyl and halo;

R^{12} and R^{14} are independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy;

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m$-C_{3-4} cycloalkyl, CN, $N(C_{1-4}$ alkyl)$_2$, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), pyrazolyl, and

morpholinyl;

alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered heterocyclic ring comprising: carbon atoms and 1-3 heteroatoms selected from N, NR^e, O, and S;

R^b is, at each occurrence, independently selected from the group consisting of: halo, OH, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl), $-O(CH_2)_m(C_{3-6}$ cycloalkyl), 4-C_{1-4} alkoxy-Ph, $-O(CH_2)_m$Ph, morpholinyl, pyridyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidinyl, pyrazinyl, and -O-pyrimidinyl;

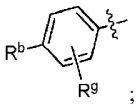
R^g is, at each occurrence, independently selected from the group consisting of: halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, and C_{1-4} haloalkoxy;

m, at each occurrence, is independently 0, 1, 2 or 3; and

s, at each occurrence, is independently 1, 2, or 3.

[0019] In a sixth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the above aspects, wherein:

R^1 is independently selected from the group consisting of: C_{1-6} alkyl, $-CONHC_{4-18}$ alkyl, $-CONH(CH_2)_{1-8}$Ph, and



;

R^6 is independently selected from the group consisting of: NH_2, $-CONH(C_{1-6}$ alkyl), $-NHCOCH_2PO(OEt)_2$, $-NHCO(CH_2)SO_2(C_{1-4}$ alkyl), R^c, OR^c, $-CONHR^c$, and $-NHCOR^c$;

R^{12} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl and C_{1-4} alkoxy;

R^{13} is independently selected from the group consisting of: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, $-(CH_2)_m$-C_{3-4} cycloalkyl, CN, $N(C_{1-4}$ alkyl$)_2$, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), pyrazolyl, and morpholinyl;

alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered saturated heterocyclic ring comprising: carbon atoms and 1-2 oxygen atoms;

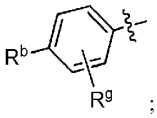
R^{14} is independently selected from the group consisting of: H and C_{1-4} alkoxy;

R^b is, at each occurrence, independently selected from the group consisting of: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl), $-O(CH_2)_m(C_{3-6}$ cycloalkyl), phenoxy, benzoxy, morpholinyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidinyl; and

R^c is, at each occurrence, independently selected from the group consisting of: C_{3-6} cycloalkyl substituted with 0-2 R^d, $-(CH_2)_m$-(phenyl substituted with 0-3 R^d), and a heteroaryl selected from: oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d.

[0020] In a seventh aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the above aspects, wherein:

R^1 is



;

R^6 is independently selected from the group consisting of: NH_2, -CONH(C_{1-4} alkyl), OPh, -CONH(C_{3-6} cycloalkyl), -CONHPh, -CONH-(2-halo-Ph), -CONH-(3-halo-Ph), -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alkyl-Ph), -CONH(4-OH-Ph), -CONH-(3-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} haloalkyl-Ph), -CONH-(4-C_{1-4} haloalkoxy-Ph), -CONH-(4-CN-Ph), -CONH-(4-tetrazolyl-Ph), -CONH-(3-halo-4-C_{1-4} alkyl-Ph), -CONH-(3-halo-4-C_{1-4} alkoxy-Ph), -CONH(CH_2)$_2$Ph, -CONH(4-(4-C_{1-4} alkoxy-Ph)-thiazol-2-yl), -CONH(1-C_{1-4} alkyl-pyrazol-3-yl), -CONH(5-C_{1-4} alkoxy-pyrid-2-yl), -CONH(6-C_{1-4} alkoxy-pyrid-3-yl), -CONH(5-C_{1-4} alkoxy-pyrazin-2-yl), -CONH(6-C_{1-4} alkoxy-pyridazin-3-yl), -NHCO(CH_2)SO_2(C_{1-4} alkyl), -NHCOPh, -NHCO(2-C_{1-4} alkyl-Ph), -NHCO(3-C_{1-4} alkyl-Ph), -NHCO(4-C_{1-4} alkyl-Ph), -NHCO(2-halo-Ph), -NHCO(3-halo-Ph), -NHCO(2-C_{1-4} haloalkyl-Ph), -NHCO(2-C_{1-4} haloalkoxy-Ph), -NHCO(2-halo-4-halo-Ph), -NHCO(2-halo-5-halo-Ph), -NHCO(oxazolyl), -NHCO(isoxazolyl), -NHCO(3-C_{1-4} alkyl-isoxazol-5-yl), -NHCO(4-C_{1-4} alkyl-isoxazol-5-yl), -NHCO(3-C_{1-4} alkoxy-isoxazol-5-yl), -NHCO(4-C_{1-4} alkoxy-isoxazol-5-yl), -NHCO(3-halo-isoxazol-5-yl), -NHCO(3-OBn-isoxazol-5-yl), -NHCO(3-(2-halo-Ph)-isoxazol-5-yl), -NHCO(3-(3-halo-Ph)-isoxazol-5-yl), -NHCO(5-C_{1-4} alkyl-1*H*-pyrazol-3-yl), imidazolyl, -NHCO(5-C_{1-4} alkyl-1,3,4-oxadiazol-2-yl), -NHCO(1-C_{1-4} alkyl-1,2,3-triazol-4-yl), -NHCO(6-C_{1-4} alkoxy-pyrid-3-yl), -NHCO(pyrazinyl), -NHCO(6-halo-pyridazin-3-yl), 5-C_{1-4} haloalkyl-1,3,4-oxadiazol-2-yl, 3-NO_2-1*H*-1,2,4-triazol-1-yl, tetrazolyl and 5-C_{1-4} alkyl-tetrazol-1-yl;

R^b is independently selected from the group consisting of: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-8} haloalkoxy, -CONH(CH_2)$_{6-20}$H, C_{3-6} cycloalkyl, C_{4-6} cycloalkenyl, -O(CH_2)$_m$(C_{3-6} cycloalkyl), phenoxy, benzoxy, pyrimidinyl, pyrazinyl and -O-pyrimidinyl; and

R^g is independently selected from the group consisting of: halo and C_{1-4} alkyl.

[0021] In an eighth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the above aspects, wherein:

R^2 is independently selected from the group consisting of: CF_3 and Me;

R^3 is independently selected from the group consisting of: H and F;

R^4 is independently selected from the group consisting of: H and F;

R^6 is independently selected from the group consisting of: NH_2, -CONHMe, OPh, -CONH(cyclopropyl), -CONH(cyclobutyl), -CONH(cyclopentyl), -CONH(cyclohexyl), -CONHPh, -CONH(4-F-Ph), -CONH(2-Cl-Ph), -CONH(4-Cl-Ph), -CONH(4-Me-Ph), -CONH(4-OH-Ph), -CONH(3-OMe-Ph), -CONH(4-OMe-Ph), -CONH(4-CF_3-Ph), -CONH(4-OCF_3-Ph), -CONH(1-Me-pyrazol-3-yl), -CONH(4-(1*H*-tetrazol-2-yl)-Ph), -CONH(4-(2*H*-tetrazol-5-yl)-Ph), -CONH(3-F-4-Me-Ph), -CONH(3-F-4-OMe-Ph), -CONH(CH_2)$_2$Ph, -CONH(5-OMe-pyrid-2-yl), -CONH(6-OMe-pyrid-3-yl), -CONH(5-OMe-pyrazin-2-yl), -CONH(6-OMe-pyridazin-3-yl), -NHCO(CH_2)SO_2Me, -NHCOPh, -NHCO(2-Me-Ph), -NHCO(3-Me-Ph), -NHCO(4-Me-Ph), -NHCO(2-Cl-Ph), -NHCO(3-Cl-Ph), -NHCO(2-Cl-4-F-Ph), -NHCO(2-Cl-5-F-Ph), -NHCO(isoxazol-5-yl), -NHCO(3-Me-isoxazol-5-yl), -NHCO(4-Me-isoxazol-5-yl), -NHCO(3-OMe-isoxazol-5-yl), -NHCO(3-Br-isoxazol-5-yl), -NHCO(3-(2-Cl-Ph)-isoxazol-5-yl), -NHCO(3-(3-F-Ph)-isoxazol-5-yl), -NHCO(3-OBn-isoxazol-5-yl), 1*H*-imidazol-1-yl, -NHCO(5-Me-1,3,4-oxadiazol-2-yl), -NHCO(1-Me-1,2,3-triazol-4-yl), -NHCO(6-OMe-pyrid-3-yl), -NHCO(6-Cl-pyridazin-3-yl), 5-CF_3-1,3,4-oxadiazol-2-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl, and 2*H*-tetrazol-5-yl;

R^{11} and R^{15} are independently selected from the group consisting of: H, Me, F, and Cl;

R^{12} is independently selected from the group consisting of: H, F, Cl, Me and OMe;

R^{13} is independently selected from the group consisting of: H, F, Cl, Br, Me, OMe, OEt, CH_2OMe, CF_3, CH_2CF_3, $OCHF_2$, OCF_3, CN, N(Me)$_2$, cyclopropyl and cyclopropylmethyl;

alternatively, R^{12} and R^{13}, together with the carbon atoms to which they are attached, combine to form a 5 to 6-membered carbocyclic ring or a 5 to 6-membered saturated heterocyclic ring comprising: carbon atoms and 1-2 oxygen atoms;

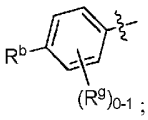
R^{14} is H;

R^b is, at each occurrence, independently selected from the group consisting of: n-pentyl, methoxy, n-butoxy, i-butoxy, i-pentoxy, -$O(CH_2)_{1-6}CF_3$, -$O(CH_2)_{1-4}CF_2CF_3$, -$CONH(CH_2)_{6-20}H$, cyclopropyl, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, -$O(CH_2)_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl; and

R^g is F.

[0022] In a ninth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the first, second, third, fourth, fifth and sixth apsects, wherein:

R^1 is



;

R^2 is independently selected from CF_3 and CH_3;

R^6 is independently selected from: R^c, -$CONHR^c$, -$NHCOR^c$, and -$NHCOCH_2SO_2$ (C_{1-4} alkyl);

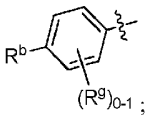
R^b is independently selected from: -$O(CH_2)_{1-6}CF_3$, -$O(CH_2)_{1-4}CF_2CF_3$, -$CONH(CH_2)_{6-20}H$, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, -$O(CH_2)_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl;

R^c is, at each occurrence, independently selected from the group consisting of: -$(CH_2)_m$-(phenyl substituted with 0-3 R^d), and a heteroaryl selected from: oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d; and

R^d is, at each occurrence, independently selected from the group consisting of: halo, OH, CN, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, tetrazolyl and OBn.

[0023] In another aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of any of the first, second, third, fourth, fifth, sixth and ninth apsects, wherein:

R^1 is



;

R^2 is independently selected from CF_3 and CH_3;

R^6 is independently selected from: R^c, -$CONHR^c$, -$NHCOR^c$, and -$NHCOCH_2SO_2$ (C_{1-4} alkyl);

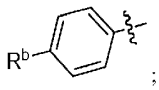
R^{11}, R^{12}, R^{14} and R^{15} are H;

R^{13} is independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; and

R^b is independently selected from: -$O(CH_2)_{1-6}CF_3$ and -$O(CH_2)_{1-4}CF_2CF_3$.

[0024] In another aspect, the present invention includes a compound of Formula (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the fourth or fifth aspect, wherein:

R^1 is



;

R^2 is independently selected from CF_3 and CH_3;

R^3 and R^4 are H;

R^6 is independently 5-membered nitrogen heteroaryl;

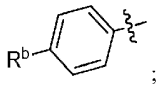
R^{11}, R^{12}, R^{14} and R^{15} are H;

R^{13} is independently selected from the group consisting of: H, C_{1-4} alkyl, C_{1-4} haloalkyl, C_{1-4} alkoxy, and C_{1-4} haloalkoxy; and

R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$ and $-O(CH_2)_{1-4}CF_2CF_3$.

[0025] In another aspect, the present invention includes a compound of Formula (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the fourth or ffith aspect, wherein:

R^1 is



;

R^2 is independently selected from CF_3 and CH_3;

R^3 and R^4 are H;

R^6 is independently selected from: 1*H*-imidazol-1-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl, and 2*H*-tetrazol-5-yl;

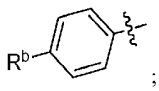
R^{11}, R^{12}, R^{14} and R^{15} are H;

R^{13} is independently selected from the group consisting of: H, Me, OMe, and $OCHF_2$; and

R^b is independently selected from: $-O(CH_2)_{1-6}CF_3$ and $-O(CH_2)_{1-4}CF_2CF_3$.

[0026] In a sixteenth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the ninth aspect, wherein:

R^1 is



;

R^6 is independently selected from the group consisting of: -CONHPh, -CONH-(4-halo-Ph), -CONH-(4-C_{1-4} alkyl -Ph), -CONH-(3-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} alkoxy-Ph), -CONH-(4-C_{1-4} haloalkyl-Ph), -CONH-(4-C_{1-4} haloalkoxy-Ph), -CONH-(3-halo-4-C_{1-4} alkoxy-Ph), $-CONH(CH_2)_2Ph$, and 2*H*-tetrazol-5-yl; and

R^b is independently selected from the group consisting of: C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, $-O(CH_2)_m(C_{3-6}$ cycloalkyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl.

[0027] In a seventeenth aspect, the present invention includes a compound of Formula (I) or (II), or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof, within the scope of the ninth aspect, wherein:

R^2 is independently selected from the group consisting of: CF_3 and Me;

R^6 is independently selected from the group consisting of: -CONHPh, -CONH-(4-F-Ph), -CONH-(4-Cl-Ph), -CONH-(4-Me-Ph), -CONH-(3-OMe-Ph), -CONH-(4-OMe-Ph), -CONH-(4-CF_3-Ph), -CONH-(4-OCF_3-Ph), -CONH-(3-F-4-OMe-Ph), -CONH$(CH_2)_2$Ph, and 2*H*-tetrazol-5-yl;

R^{11} and R^{15} are independently selected from the group consisting of: H and F;

R^{12} is independently selected from the group consisting of: H, Me and OMe;

R^{13} is independently selected from the group consisting of: H, F, Cl, Me, OMe, OEt, CF_3, $OCHF_2$, OCF_3 and CN;

R^{14} is H; and

R^b is independently selected from the group consisting of: n-pentyl, methoxy, n-butoxy, i-butoxy, -O$(CH_2)_{1-3}CF_3$, -O$(CH_2)_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl and -O-pyrimidin-2-yl.

[0028] In an eighteenth aspect, the present invention provides a compound selected from the exemplified examples or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[0029] In another aspect, the present invention provides a compound selected from any subset list of compounds or a single compound from the exemplified examples within the scope of any of the above aspects.

[0030] In another aspect, the present disclosure provides a compound selected from:

(*S*)-3-(1*H*-tetrazol-5-yl)-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-N-(4-methoxyphenyl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-3-(2*H*-tetrazol-5-yl)-4-(p-tolyl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-N-(4-(trifluoromethoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-(6-methoxypyridin-3-yl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-cyclopropyl-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-N-(4-hydroxyphenyl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide,

(*S*)-4-(4-(difluoromethoxy)phenyl)-3-(1*H*-tetrazol-1-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-3-methyl-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)isoxazole-5-carboxamide,

(*S*)-5-methyl-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)-1,3,4-oxadiazole-2-carboxamide,

N^2-heptyl-N^5-(4-methoxyphenyl)-2-methyl-6-oxo-4-(p-tolyl)-1,2,3,6-tetrahydropyridine-2,5-dicarboxamide,

(*S*)-3-(1*H*-tetrazol-1-yl)-4-(p-tolyl)-6-(4-((6,6,6-trifluorohexyl)oxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-4-(5,6,7,8-tetrahydronaphthalen-2-yl)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one,

(*S*)-2-(methylsulfonyl)-N-(2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)acetamide,

(*S*)-3-(1*H*-tetrazol-5-yl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-4-(4-(2,2,2-trifluoroethyl)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one, and

(*S*)-N-(5-methoxypyrazin-2-yl)-2-oxo-4-(p-tolyl)-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide; or a pharmaceutically acceptable salt thereof.

[0031] In another embodiment, R^1 is independently -CONH(C_{4-18} alkyl), -CONHC_{2-8} haloalkyl, or -CONH$(CH_2)_{1-8}$Ph.

[0032] In another embodiment, R^1 is -$(CH_2)_m$-(C_{3-10} carbocycle substituted with 0-2 R^b and 0-2 R^g), or -$(CH_2)_m$-(5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g).

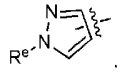
[0033] In another embodiment, R^1 is -$(CH_2)_m$-(C_{3-10} carbocycle substituted with 0-2 R^b and 0-2 R^g).

[0034] In another embodiment, R^1 is -$(CH_2)_m$-(phenyl substituted with 0-2 R^b and 0-2 R^g).

[0035] In another embodiment, R^1 is -$(CH_2)_m$-(5- to 6-membered heteroaryl comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O and S; wherein said heteroaryl is substituted with 0-1 R^b and 0-2 R^g).

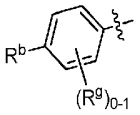
[0036] In another embodiment, R^1 is a C_{1-12} hydrocarbon chain substituted with 0-3 R^a; wherein said hydrocarbon chain may be straight or branched, saturated or unsaturated.

[0037] In another embodiment, R^1 is independently: C_{1-6} alkyl, C_{3-6} cycloalkyl, -CONHC_{4-18} alkyl, -CONHC_{2-8} haloalkyl, -CONH$(CH_2)_{1-8}$ Ph, -$(CH_2)_m$-(phenyl substituted with 1 R^b and 0-2 R^g), or a 5- to 6-membered heteroaryl substituted with 0-1 R^b and 0-2 R^g, wherein said heteroaryl is selected from: pyridyl, oxazolyl, thiazolyl and

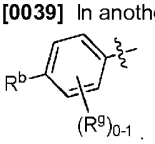


.

[0038] In another embodiment, R^1 is independently: C_{1-6} alkyl, -CONHC_{4-18} alkyl, -CONH$(CH_2)_{1-8}$Ph, or

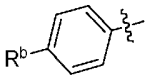


[0039] In another embodiment, R^1 is



.

[0040] In another embodiment, R^1 is independently



[0041] In another embodiment, R^2 is independently C_{1-4} alkyl or C_{1-4} haloalkyl.

[0042] In another embodiment, R^2 is C_{1-4} alkyl.

[0043] In another embodiment, R^2 is C_{1-4} haloalkyl.

[0044] In another embodiment, R^2 is independently CF_3 or Me.

[0045] In another embodiment, R^2 is CF_3.

[0046] In another embodiment, R^2 is Me.

[0047] In another embodiment, R^3 is independently H or F.

[0048] In another embodiment, R^3 is H.

[0049] In another embodiment, R^3 is F.

[0050] In another embodiment, R^4 is independently H or F.

[0051] In another embodiment, R^4 is H.

[0052] In another embodiment, R^4 is F.

[0053] In another embodiment, R^5 is independently H or F.

[0054] In another embodiment, R^5 is H.

[0055] In another embodiment, R^5 is F.

[0056] In another embodiment, R^6 is independently C_{1-4} alkyl, R^c, or $-(CH_2)_n-(X)_t-(CH2)_mR^c$.

[0057] In another embodiment, R^6 is independently -CONH(C_{1-6} alkyl), $-NHCOX_1SO_2R^j$, $-NHCOCOR^j$, $-NHCOCH(OH)R^j$, $-NHCOCH_2COR^j$, $-NHCONHR^j$, or $-OCONR^fR^j$.

[0058] In another embodiment, R^6 is independently NH_2, -CONH(C_{1-6} alkyl), R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, $-NHCO(CH_2)SO_2$(C_{1-4} alkyl), -NHCOCO(C_{1-4} alkyl), -NHCOCH(OH)(C_{1-4} alkyl), $-NHCOCH_2CO$(C_{1-4} alkyl), -NHCONH(C_{1-4} alkyl), or -OCONH(C_{1-4} alkyl).

[0059] In another embodiment, R^6 is independentlyNH_2, -CONH(C_{1-6} alkyl), $-NHCO(CH_2)SO_2$(C_{1-4} alkyl), R^c, OR^c, $-CONHR^c$, or $-NHCOR^c$.

[0060] In another embodiment, R^6 is independently NH_2, -CONH(C_{1-6} alkyl), $-NHCO(CH_2)SO_2$(C_{1-4} alkyl), R^c, OR^c, $-CONHR^c$, or $-NHCOR^c$.

[0061] In another embodiment, R^6 is independently R^c, $-CONHR^c$, $-NHCOR^c$, or-$NHCOCH_2SO_2$ (C_{1-4} alkyl).

[0062] In another embodiment, R^6 is independently 5-membered nitrogen heteroaryl.

[0063] In another embodiment, R^6 is independently: 1*H*-imidazol-1-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl, or 2*H*-tetrazol-5-yl.

[0064] In another embodiment, R^{11} is independently H, C_{1-4} alkyl or halo.

[0065] In another embodiment, R^{11} is independently H, Me, F, or Cl.

[0066] In another embodiment, R^{11} is H.

[0067] In another embodiment, R^{11} is C_{1-4} alkyl.

[0068] In another embodiment, R^{11} is Me.

[0069] In another embodiment, R^{11} is halo.

[0070] In another embodiment, R^{11} is independently F or Cl.

[0071] In another embodiment, R^{12} is independently H, halo, C_{1-4} alkyl or C_{1-4} alkoxy.

[0072] In another embodiment, R^{12} is independently H, F, Cl, Me and OMe.

[0073] In another embodiment, R^{12} is H.

[0074] In another embodiment, R^{12} is C_{1-4} alkyl.

[0075] In another embodiment, R^{12} is Me.

[0076] In another embodiment, R^{12} is C_{1-4} alkoxy.

[0077] In another embodiment, R^{12} is OMe.

[0078] In another embodiment, R^{12} is halo.

[0079] In another embodiment, R^{12} is independently F or Cl.

[0080] In another embodiment, R^{13} is independently: H, halo, C_{1-4} alkyl substituted with 0-1 R^i, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, C_{3-4} cycloalkyl, CN, NR^fR^j, SR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), or a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S.

[0081] In another embodiment, R^{13} is independently: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN, C_{3-4} cycloalkyl, $N(C_{1-4}$ alkyl)$_2$, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), pyrazolyl, or morpholinyl.

[0082] In another embodiment, R^{13} is independently: H, halo, C_{1-4} alkyl substituted with 0-1 C_{1-4} alkoxy, C_{1-4} alkoxy, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, CN or C_{3-4} cycloalkyl.

[0083] In another embodiment, R^{13} is independently: NR^fR^j, $NHCO_2(C_{1-4}$ alkyl), $NHSO_2(C_{1-4}$ alkyl), or a 4- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S.

[0084] In another embodiment, R^{14} is independently H, halo, C_{1-4} alkyl or C_{1-4} alkoxy.

[0085] In another embodiment, R^{14} is independently H, F, Cl, Me and OMe.

[0086] In another embodiment, R^{14} is H.

[0087] In another embodiment, R^{14} is C_{1-4} alkyl.

[0088] In another embodiment, R^{14} is Me.

[0089] In another embodiment, R^{14} is C_{1-4} alkoxy.

[0090] In another embodiment, R^{14} is OMe.

[0091] In another embodiment, R^{14} is halo.

[0092] In another embodiment, R^{14} is independently F or Cl.

[0093] In another embodiment, R^{15} is independently H, C_{1-4} alkyl or halo.

[0094] In another embodiment, R^{15} is independently H, Me, F, or Cl.

[0095] In another embodiment, R^{15} is H.

[0096] In another embodiment, R^{15} is C_{1-4} alkyl.

[0097] In another embodiment, R^{15} is Me.

[0098] In another embodiment, R^{15} is halo.

[0099] In another embodiment, R^{15} is independently F or Cl.

[0100] In another embodiment, R^{16} is H.

[0101] In another embodiment, R^{16} is C_{1-4} alkyl.

[0102] In another embodiment, X is independently O, S, or NH.

[0103] In another embodiment, X is independently O or S.

[0104] In another embodiment, X is O.

[0105] In another embodiment, X is independently CONH or NHCO.

[0106] In another embodiment, X is CONH.

[0107] In another embodiment, X is NHCO.

[0108] In another embodiment, R^b is, at each occurrence, independently: C_{1-10} alkyl, C_{1-10} alkoxy, C_{1-1} haloalkyl, C_{1-1} haloalkoxy, C_{1-1} alkylthio, C_{1-10} haloalkyltho, $-CONH(CH_2)_{4-20}H$, $-O(CH_2)_sO(C_{1-6}$ alkyl), R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$, or $-(CH_2)_n-(CH_2O)_m-CH_2)_nR^f$.

[0109] In another embodiment, R^b is, at each occurrence, independently: halo, OH, C_{1-8} alkyl, C_{1-8} alkoxy, C_{1-8} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $N(C_{1-4}$ alkyl$)_2$, $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl), $-O(CH_2)_m(C_{3-6}$ cycloalkyl), 4-C_{1-4} alkoxy-Ph, $-O(CH_2)_m$Ph, morpholinyl, pyridyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidinyl, pyrazinyl, or -O-pyrimidinyl.

[0110] In another embodiment, R^b is, at each occurrence, independently: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-10} haloalkoxy, $-O(CH_2)_sO(C_{1-6}$ alkyl), $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$ cycloalkyl), $-(CH_2)_m(C_{4-6}$ cycloalkenyl), $-O(CH_2)_m(C_{3-6}$ cycloalkyl), phenoxy, benzoxy, morpholinyl, 2-C_{1-4} alkoxy-pyridin-5-yl, pyrimidin-5-yl, pyrazin-2-yl or -O-pyrimidinyl.

[0111] In another embodiment, R^b is, at each occurrence, independently: halo, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} haloalkyl, C_{1-8} haloalkoxy, $-CONH(CH_2)_{6-20}H$, C_{3-6} cycloalkyl, C_{4-6} cycloalkenyl, $-O(CH_2)_m(C_{3-6}$ cycloalkyl), phenoxy, benzoxy, pyrimidinyl, pyrazinyl and -O-pyrimidinyl.

[0112] In another embodiment, R^b is, at each occurrence, independently: $-O(CH_2)_{1-6}CF_3$ and $-O(CH_2)_{1-4}CF_2CF_3$.

[0113] In another embodiment, R^c is, at each occurrence, independently: C_{3-6} cycloalkyl substituted with 0-2 R^d, C_{3-6} cycloalkenyl substituted with 0-2 R^d, or $-(CH_2)_m$-(phenyl substituted with 0-3 R^d).

[0114] In another embodiment, R^c is, at each occurrence, independently: C_{3-6} cycloalkyl substituted with 0-2 R^d or C_{3-6} cycloalkenyl substituted with 0-2 R^d.

[0115] In another embodiment, R^c is, at each occurrence, independently $-(CH_2)_m$-(phenyl substituted with 0-3 R^d),.

[0116] In another embodiment, R^c is, at each occurrence, independently C_{3-6} cycloalkyl substituted with 0-2 R^d.

[0117] In another embodiment, R^c is, at each occurrence, independently C_{3-6} cycloalkenyl substituted with 0-2 R^d.

[0118] In another embodiment, R^c is, at each occurrence, independently a 5- to 6-membered heterocycle comprising: carbon atoms and 1-4 heteroatoms selected from N, NR^e, O, and S; wherein said heterocycle is substituted with 0-2 R^d.

[0119] In another embodiment, R^c is, at each occurrence, independently $-(CH_2)_m$-(phenyl substituted with 0-3 R^d), or a heteroaryl selected from: oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d.

[0120] In another embodiment, R^c is, at each occurrence, independently a heteroaryl selected from: oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, and pyrazinyl; wherein said heteroaryl is substituted with 0-2 R^d.

[0121] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 10 μM, using the MGAT2 SPA assay.

[0122] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 5 μM, using the MGAT2 SPA assay.

[0123] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 1 μM, using the MGAT2 SPA assay.

[0124] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 0.5 μM, using the MGAT2 SPA assay.

[0125] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 10 μM, using the MGAT2 LCMS assay.

[0126] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 5 μM, using the MGAT2 LCMS assay.

[0127] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 2.5 μM, using the MGAT2 LCMS assay.

[0128] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 1 μM, using the MGAT2 LCMS assay.

[0129] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 0.5 μM, using the MGAT2 LCMS assay.

[0130] In another embodiment, the compounds of the present invention have hMGAT2 IC_{50} values ≤ 0.1 μM, using the MGAT2 LCMS assay.

II. OTHER EMBODIMENTS OF THE INVENTION

[0131] In another embodiment, the present invention provides a composition comprising at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[0132] In another embodiment, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[0133] In another embodiment, the present invention provides a pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[0134] In another embodiment, the present invention provides a process for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[0135] In another embodiment, the present invention provides an intermediate for making a compound of the present invention or a stereoisomer, a tautomer, a pharmaceutically acceptable salt, or a solvate thereof.

[0136] In another embodiment, the present invention provides a pharmaceutical composition further comprising additional therapeutic agent(s). In a preferred embodiment, the present invention provides pharmaceutical composition, wherein the additional therapeutic agent is, for example, a dipeptidyl peptidase-IV (DPP4) inhibitor (for example a member selected from saxagliptin, sitagliptin, vildagliptin and alogliptin).

[0137] In another embodiment, the present invention provides at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent for use in the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

[0138] Examples of diseases or disorders associated with the activity of the MGAT2 that can be prevented, modulated, or treated using compounds according to the present invention include, but are not limited to, diabetes, hyperglycemia, impaired glucose tolerance, gestational diabetes, insulin resistance, hyperinsulinemia, nonalcoholic fatty liver disease (NAFLD) including nonalcoholic steatohepatitis (NASH), retinopathy, neuropathy, nephropathy, delayed wound healing, atherosclerosis and its sequelae, abnormal heart function, myocardial ischemia, stroke, Metabolic Syndrome, hypertension, obesity, dyslipidemia, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low high-density lipoprotein (HDL), high low-density lipoprotein (LDL), non-cardiac ischemia, lipid disorders, and glaucoma.

[0139] In another embodiment, the present invention provides at least one of the compounds of the present invention, alone, or,

optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent, for use in the treatment and/or prophylaxis of diabetes, hyperglycemia, gestational diabetes, obesity, dyslipidemia, and hypertension.

[0140] In another embodiment, the present invention provides at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent, for use in the treatment and/or prophylaxis of diabetes.

[0141] In another embodiment, the present invention provides at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent, for use in the treatment and/or prophylaxis of hyperglycemia.

[0142] In another embodiment, the present invention provides at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent, for use in the treatment and/or prophylaxis of obesity.

[0143] In another embodiment, the present invention provides at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent, for use in the treatment and/or prophylaxis of dyslipidemia.

[0144] In another embodiment, the present invention provides a at least one of the compounds of the present invention, alone, or, optionally, in combination with another compound of the present invention and/or at least one other type of therapeutic agent, for use in the treatment and/or prophylaxis of hypertension.

[0145] In another embodiment, the present invention provides a compound of the present invention for use in therapy.

[0146] In another embodiment, the present invention provides a compound of the present invention for use in therapy for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

[0147] In another embodiment, the present invention also provides the use of a compound of the present invention for the manufacture of a medicament for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

[0148] In another embodiment, the present invention provides a first and second therapeutic agent for use in the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2, wherein the first therapeutic agent is a compound of the present invention. Preferably, the second therapeutic agent, is for example, a dipeptidyl peptidase-IV (DPP4) inhibitor (for example a member selected from saxagliptin, sitagliptin, vildagliptin, linagliptin and alogliptin).

[0149] In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in therapy.

[0150] In another embodiment, the present invention provides a combined preparation of a compound of the present invention and additional therapeutic agent(s) for simultaneous, separate or sequential use in the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2.

[0151] Where desired, the compound of the present invention may be used in combination with one or more other types of antidiabetic agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection. The other type of antidiabetic agent that may be optionally employed in combination with the MGAT2 inhibitor of the present invention may be one, two, three or more antidiabetic agents or antihyperglycemic agents which may be administered orally in the same dosage form, in a separate oral dosage form, or by injection to produce an additional pharmacological benefit.

[0152] The antidiabetic agents used in the combination with the MGAT2 inhibitor of the present invention include, but are not limited to, insulin secretagogues or insulin sensitizers, other MGAT2 inhibitors, or other antidiabetic agents. These agents include, but are not limited to, dipeptidyl peptidase IV (DP4) inhibitors (for example, sitagliptin, saxagliptin, alogliptin, linagliptin and vildagliptin), biguanides (for example, metformin and phenformin), sulfonyl ureas (for example, glyburide, glimepiride and glipizide), glucosidase inhibitors (for example, acarbose, miglitol), PPARγ agonists such as thiazolidinediones (for example, rosiglitazone and pioglitazone), PPAR α/γ dual agonists (for example, muraglitazar, tesaglitazar and aleglitazar), glucokinase activators, GPR40 receptor modulators (e.g. TAK-875), GPR119 receptor modulators (for example, MBX-2952, PSN821, and APD597), sodium-glucose transporter-2 (SGLT2) inhibitors (for example, dapagliflozin, canagliflozin and remagliflozin), 11b-HSD-

1 inhibitors (for example MK-0736, BI35585, BMS-823778, and LY2523199), amylin analogs such as pramlintide, and/or insulin.

[0153] The MGAT2 inhibitor of the present invention may also be optionally employed in combination with one or more hypophagic and/or weight-loss agents such as diethylpropion, phendimetrazine, phentermine, orlistat, sibutramine, lorcaserin, pramlintide, topiramate, MCHR1 receptor antagonists, oxyntomodulin, naltrexone, Amylin peptide, NPY Y5 receptor modulators, NPY Y2 receptor modulators, NPY Y4 receptor modulators, cetilistat, 5HT2c receptor modulators, and the like. The compounds of the present invention may also be employed in combination with an agonist of the glucagon-like peptide-1 receptor (GLP-1 R), such as exenatide, liraglutide, GPR-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37), which may be administered via injection, intranasal, or by transdermal or buccal devices.

[0154] The MGAT2 inhibitor of the present invention may also be optionally employed in combination with one or more other types of therapeutic agents, such as DGAT inhibitors, LDL lowering drugs such as statins (inhibitors of HMG CoA reductase) or inhibitors of cholesterol absorption, modulators of PCSK9, drugs that increase HDL such as CETP inhibitors.

[0155] This invention encompasses all combinations of preferred aspects of the invention noted herein. It is understood that any and all embodiments of the present invention may be taken in conjunction with any other embodiment or embodiments to describe additional embodiments. It is also understood that each individual element of the embodiments is its own independent embodiment. Furthermore, any element of an embodiment is meant to be combined with any and all other elements from any embodiment to describe an additional embodiment.

III. CHEMISTRY

[0156] Throughout the specification and the appended claims, a given chemical formula or name shall encompass all stereo and optical isomers and racemates thereof where such isomers exist. Unless otherwise indicated, all chiral (enantiomeric and diastereomeric) and racemic forms are within the scope of the invention. Many geometric isomers of C=C double bonds, C=N double bonds, ring systems, and the like can also be present in the compounds, and all such stable isomers are contemplated in the present invention. Cis- and trans- (or *E*- and *Z*-) geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. The present compounds can be isolated in optically active or racemic forms. Optically active forms may be prepared by resolution of racemic forms or by synthesis from optically active starting materials. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention. When enantiomeric or diastereomeric products are prepared, they may be separated by conventional methods, for example, by chromatography or fractional crystallization. Depending on the process conditions the end products of the present invention are obtained either in free (neutral) or salt form. Both the free form and the salts of these end products are within the scope of the invention. If so desired, one form of a compound may be converted into another form. A free base or acid may be converted into a salt; a salt may be converted into the free compound or another salt; a mixture of isomeric compounds of the present invention may be separated into the individual isomers. Compounds of the present invention, free form and salts thereof, may exist in multiple tautomeric forms, in which hydrogen atoms are transposed to other parts of the molecules and the chemical bonds between the atoms of the molecules are consequently rearranged. It should be understood that all tautomeric forms, insofar as they may exist, are included within the invention.

[0157] As used herein, the term "alkyl" or "alkylene" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For examples, "C_1 to C_{12} alkyl" or "C_{1-12} alkyl" (or alkylene), is intended to include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} and C_{12} alkyl groups; "C_4 to C_{18} alkyl" or "C_{4-18} alkyl" (or alkylene), is intended to include C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11}, C_{12}, C_{13}, C_{14}, C_{15}, C_{16}, C_{17}, and C_{18} alkyl groups. Additionally, for example, "C_1 to C_6 alkyl" or "C_{1-6} alkyl" denotes alkyl having 1 to 6 carbon atoms. Alkyl group can be unsubstituted or substituted with at least one hydrogen being replaced by another chemical group. Example alkyl groups include, but are not limited to, methyl (Me), ethyl (Et), propyl (*e.g.,* n-propyl and isopropyl), butyl (*e.g.,* n-butyl, isobutyl, *t*-butyl), and pentyl (*e.g.*, n-pentyl, isopentyl, neopentyl). When "C_0 alkyl" or "C_0 alkylene" is used, it is intended to denote a direct bond.

[0158] Alkenyl" or "alkenylene" is intended to include hydrocarbon chains of either straight or branched configuration having the specified number of carbon atoms and one or more, preferably one to two, carbon-carbon double bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkenyl" or "C_{2-6} alkenyl" (or alkenylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkenyl groups. Examples of alkenyl include, but are not limited to, ethenyl, 1-propenyl, 2-propenyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3, pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-methyl-2-propenyl, and 4-methyl-3-pentenyl.

[0159] "Alkynyl" or "alkynylene" is intended to include hydrocarbon chains of either straight or branched configuration having one or more, preferably one to three, carbon-carbon triple bonds that may occur in any stable point along the chain. For example, "C_2 to C_6 alkynyl" or "C_{2-6} alkynyl" (or alkynylene), is intended to include C_2, C_3, C_4, C_5, and C_6 alkynyl groups; such as ethynyl, propynyl, butynyl, pentynyl, and hexynyl.

[0160] When the term "hydrocarbon chain" is used, it is intended to include "alkyl", "alkenyl" and "alkynyl", unless otherwise specified.

[0161] The term "alkoxy" or "alkyloxy" refers to an -O-alkyl group. For example, "C_1 to C_6 alkoxy" or "C_{1-6} alkoxy" (or alkyloxy), is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 alkoxy groups. Example alkoxy groups include, but are not limited to, methoxy, ethoxy, propoxy (*e.g.*, n-propoxy and isopropoxy), and *t*-butoxy. Similarly, "alkylthio" or "thioalkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example methyl-S- and ethyl-S-.

[0162] "Halo" or "halogen" includes fluoro, chloro, bromo, and iodo. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogens. Examples of haloalkyl include, but are not limited to, fluoromethyl, difluoromethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, pentachloroethyl, 2,2,2-trifluoroethyl, heptafluoropropyl, and heptachloropropyl. Examples of haloalkyl also include "fluoroalkyl" that is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more fluorine atoms.

[0163] "Haloalkoxy" or "haloalkyloxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. For example, "C_{1-6} haloalkoxy", is intended to include C_1, C_2, C_3, C_4, C_5, and C_6 haloalkoxy groups. Examples of haloalkoxy include, but are not limited to, trifluoromethoxy, 2,2,2-trifluoroethoxy, and pentafluorothoxy. Similarly, "haloalkylthio" or "thiohaloalkoxy" represents a haloalkyl group as defined above with the indicated number of carbon atoms attached through a sulphur bridge; for example trifluoromethyl-S-, and pentafluoroethyl-S-.

[0164] The term "cycloalkyl" refers to cyclized alkyl groups, including mono-, bi- or poly-cyclic ring systems. For example, "C_3 to C_6 cycloalkyl" or "C_{3-6} cycloalkyl" is intended to include C_3, C_4, C_5, and C_6 cycloalkyl groups. Example cycloalkyl groups include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and norbornyl. Branched cycloalkyl groups such as 1-methylcyclopropyl and 2-methylcyclopropyl are included in the definition of "cycloalkyl". The term "cycloalkenyl" refers to cyclized alkenyl groups. C_{4-6} cycloalkenyl is intended to include C_4, C_5, and C_6 cycloalkenyl groups. Example cycloalkenyl groups include, but are not limited to, cyclobutenyl, cyclopentenyl, and cyclohexenyl.

[0165] As used herein, "carbocycle," "carbocyclyl," or "carbocyclic residue" is intended to mean any stable 3-, 4-, 5-, 6-, 7-, or 8-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, or 13-membered bicyclic or tricyclic ring, any of which may be saturated, partially unsaturated, unsaturated or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, anthracenyl, and tetrahydronaphthyl (tetralin). As shown above, bridged rings are also included in the definition of carbocycle (*e.g.*, [2.2.2]bicyclooctane). Preferred carbocycles, unless otherwise specified, are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, indanyl, and tetrahydronaphthyl. When the term "carbocycle" is used, it is intended to include "aryl." A bridged ring occurs when one or more, preferably one to three, carbon atoms link two non-adjacent carbon atoms. Preferred bridges are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[0166] As used herein, the term "bicyclic carbocycle" or "bicyclic carbocyclic group" is intended to mean a stable 9- or 10-membered carbocyclic ring system that contains two fused rings and consists of carbon atoms. Of the two fused rings, one ring is a benzo ring fused to a second ring; and the second ring is a 5- or 6-membered carbon ring which is saturated, partially unsaturated, or unsaturated. The bicyclic carbocyclic group may be attached to its pendant group at any carbon atom which results in a stable structure. The bicyclic carbocyclic group described herein may be substituted on any carbon if the resulting compound is stable. Examples of a bicyclic carbocyclic group are, but not limited to, naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and indanyl.

[0167] "Aryl" groups refer to monocyclic or bicyclic aromatic hydrocarbons, including, for example, phenyl, and naphthyl. Aryl moieties are well known and described, for example, in Hawley's Condensed Chemical Dictionary (15th ed.), R.J. Lewis, ed., J.

Wiley & Sons, Inc., New York, 2007. "C_{6-10} aryl" refers to phenyl and naphthyl.

[0168] The term "benzyl," as used herein, refers to a methyl group on which one of the hydrogen atoms is replaced by a phenyl group.

[0169] As used herein, the term "heterocycle," "heterocyclyl," or "heterocyclic group" is intended to mean a stable 3-, 4-, 5-, 6-, or 7-membered monocyclic or bicyclic or 7-, 8-, 9-, 10-, 11-, 12-, 13-, or 14-membered polycyclic heterocyclic ring that is saturated, partially unsaturated, or fully unsaturated, and that contains carbon atoms and 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S; and including any polycyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2). The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom that results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. When the term "heterocycle" is used, it is intended to include heteroaryl.

[0170] Examples of heterocycles include, but are not limited to, acridinyl, azetidinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazolinyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-ca*rbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, imidazolopyridinyl, indolenyl, indolinyl, indolizinyl, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isothiazolopyridinyl, isoxazolyl, isoxazolopyridinyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolopyridinyl, oxazolidinylperimidinyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolopyridinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2-pyrrolidonyl, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrazolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thiazolopyridinyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[0171] Examples of 5- to 10-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, triazolyl, benzimidazolyl, 1*H*-indazolyl, benzofuranyl, benzothiofuranyl, benztetrazolyl, benzotriazolyl, benzisoxazolyl, benzoxazolyl, oxindolyl, benzoxazolinyl, benzthiazolyl, benzisothiazolyl, isatinoyl, isoquinolinyl, octahydroisoquinolinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, isoxazolopyridinyl, quinazolinyl, quinolinyl, isothiazolopyridinyl, thiazolopyridinyl, oxazolopyridinyl, imidazolopyridinyl, and pyrazolopyridinyl.

[0172] Examples of 5- to 6-membered heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, piperazinyl, piperidinyl, imidazolyl, imidazolidinyl, indolyl, tetrazolyl, isoxazolyl, morpholinyl, oxazolyl, oxadiazolyl, oxazolidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

[0173] As used herein, the term "bicyclic heterocycle" or "bicyclic heterocyclic group" is intended to mean a stable 9- or 10-membered heterocyclic ring system which contains two fused rings and consists of carbon atoms and 1, 2, 3, or 4 heteroatoms independently selected from the group consisting of N, O and S. Of the two fused rings, one ring is a 5- or 6-membered monocyclic aromatic ring comprising a 5-membered heteroaryl ring, a 6-membered heteroaryl ring or a benzo ring, each fused to a second ring. The second ring is a 5- or 6-membered monocyclic ring which is saturated, partially unsaturated, or unsaturated, and comprises a 5-membered heterocycle, a 6-membered heterocycle or a carbocycle (provided the first ring is not benzo when the second ring is a carbocycle).

[0174] The bicyclic heterocyclic group may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The bicyclic heterocyclic group described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then

these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1.

[0175] Examples of a bicyclic heterocyclic group are, but not limited to, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, indolyl, isoindolyl, indolinyl, 1*H*-indazolyl, benzimidazolyl, 1,2,3,4-tetrahydroquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, 5,6,7,8-tetrahydro-quinolinyl, 2,3-dihydro-benzofuranyl, chromanyl, 1,2,3,4-tetrahydro-quinoxalinyl, and 1,2,3,4-tetrahydro-quinazolinyl.

[0176] As used herein, the term "aromatic heterocyclic group" or "heteroaryl" is intended to mean stable monocyclic and polycyclic aromatic hydrocarbons that include at least one heteroatom ring member such as sulfur, oxygen, or nitrogen. Heteroaryl groups include, without limitation, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, furyl, quinolyl, isoquinolyl, thienyl, imidazolyl, thiazolyl, indolyl, pyrroyl, oxazolyl, benzofuryl, benzothienyl, benzthiazolyl, isoxazolyl, pyrazolyl, triazolyl, tetrazolyl, indazolyl, 1,2,4-thiadiazolyl, isothiazolyl, purinyl, carbazolyl, benzimidazolyl, indolinyl, benzodioxolanyl, and benzodioxane. Heteroaryl groups are substituted or unsubstituted. The nitrogen atom is substituted or unsubstituted (*i.e.*, N or NR wherein R is H or another substituent, if defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and $S(O)_p$, wherein p is 0, 1 or 2).

[0177] Examples of 5- to 6-membered heteroaryls include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrazinyl, imidazolyl, imidazolidinyl, tetrazolyl, isoxazolyl, oxazolyl, oxadiazolyl, oxazolidinyl, thiadiazinyl, thiadiazolyl, thiazolyl, triazinyl, and triazolyl.

[0178] Bridged rings are also included in the definition of heterocycle. A bridged ring occurs when one or more, preferably one to three, atoms (*i.e.*, C, O, N, or S) link two non-adjacent carbon or nitrogen atoms. Examples of bridged rings include, but are not limited to, one carbon atom, two carbon atoms, one nitrogen atom, two nitrogen atoms, and a carbon-nitrogen group. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring. When a ring is bridged, the substituents recited for the ring may also be present on the bridge.

[0179] The term "counter ion" is used to represent a negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate or a positively charged species such as sodium (Na+), potassium (K+), ammonium (R_nNH_m+ where n=0-4 and m=0-4) and the like.

[0180] When a dotted ring is used within a ring structure, this indicates that the ring structure may be saturated, partially saturated or unsaturated.

[0181] As used herein, the term "amine protecting group" means any group known in the art of organic synthesis for the protection of amine groups which is stable to an ester reducing agent, a disubstituted hydrazine, R4-M and R7-M, a nucleophile, a hydrazine reducing agent, an activator, a strong base, a hindered amine base and a cyclizing agent. Such amine protecting groups fitting these criteria include those listed in Wuts, P. G. M. and Greene, T.W. Projecting Groups in Organic Synthesis, 4th Edition, Wiley (2007) and The Peptides: Analysis, Synthesis, Biology, Vol. 3, Academic Press, New York (1981). Examples of amine protecting groups include, but are not limited to, the following: (1) acyl types such as formyl, trifluoroacetyl, phthalyl, and p-toluenesulfonyl; (2) aromatic carbamate types such as benzyloxycarbonyl (Cbz) and substituted benzyloxycarbonyls, 1-(p-biphenyl)-1-methylethoxycarbonyl, and 9-fluorenylmethyloxycarbonyl (Fmoc); (3) aliphatic carbamate types such as *tert*-butyloxycarbonyl (Boc), ethoxycarbonyl, diisopropylmethoxycarbonyl, and allyloxycarbonyl; (4) cyclic alkyl carbamate types such as cyclopentyloxycarbonyl and adamantyloxycarbonyl; (5) alkyl types such as triphenylmethyl and benzyl; (6) trialkylsilane such as trimethylsilane; (7) thiol containing types such as phenylthiocarbonyl and dithiasuccinoyl; and (8) alkyl types such as triphenylmethyl, methyl, and benzyl; and substituted alkyl types such as 2,2,2-trichloroethyl, 2-phenylethyl, and *t*-butyl; and trialkylsilane types such as trimethylsilane.

[0182] As referred to herein, the term "substituted" means that at least one hydrogen atom is replaced with a non-hydrogen group, provided that normal valencies are maintained and that the substitution results in a stable compound. Ring double bonds, as used herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N, or N=N).

[0183] In cases wherein there are nitrogen atoms (*e.g.*, amines) on compounds of the present invention, these may be converted to N-oxides by treatment with an oxidizing agent (e.g., mCPBA and/or hydrogen peroxides) to afford other compounds of this invention. Thus, shown and claimed nitrogen atoms are considered to cover both the shown nitrogen and its N-oxide (N→O) derivative.

[0184] When any variable occurs more than one time in any constituent or formula for a compound, its definition at each

occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-3 R, then said group may optionally be substituted with up to three R groups, and at each occurrence R is selected independently from the definition of R.

[0185] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom in which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent.

[0186] Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[0187] The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms that are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, and/or other problem or complication, commensurate with a reasonable benefit/risk ratio.

[0188] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, and isethionic, and the like.

[0189] The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound that contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in Remington: The Science and Practice of Pharmacy, 22nd Edition, Allen, L. V. Jr., Ed.; Pharmaceutical Press, London, UK (2012).

[0190] The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include deuterium and tritium. Isotopes of carbon include ^{13}C and ^{14}C. Isotopically-labeled compounds of the invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described herein, using an appropriate isotopically-labeled reagent in place of the non-labeled reagent otherwise employed.

[0191] The term "solvate" means a physical association of a compound of this invention with one or more solvent molecules, whether organic or inorganic. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. The solvent molecules in the solvate may be present in a regular arrangement and/or a non-ordered arrangement. The solvate may comprise either a stoichiometric or nonstoichiometric amount of the solvent molecules. "Solvate" encompasses both solution-phase and isolable solvates. Exemplary solvates include, but are not limited to, hydrates, ethanolates, methanolates, and isopropanolates. Methods of solvation are generally known in the art.

[0192] Abbreviations as used herein, are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "L" for liter or liters, "mL" for milliliter or milliliters, "µL" for microliter or microliters, "N" for normal, "M" for molar, "mmol" for millimole or millimoles, "min" for minute or min, "h" for hour or h, "rt" for room temperature, "RT" for retention time, "atm" for atmosphere, "psi" for pounds per square inch, "conc." for concentrate, "aq" for "aqueous", "sat" or "sat'd " for saturated, "MW" for molecular weight, "mp" for melting point, "MS" or "Mass Spec" for mass spectrometry, "ESI" for electrospray ionization mass spectroscopy, "HR" for high resolution, "HRMS" for high resolution mass spectrometry, "LCMS" for liquid chromatography mass spectrometry, "HPLC" for high pressure liquid chromatography, "RP HPLC" for reverse phase HPLC, "TLC" or "tlc" for thin layer chromatography, "NMR" for nuclear magnetic resonance spectroscopy, "nOe" for nuclear Overhauser effect spectroscopy, "^{1}H" for proton, "δ" for delta, "s" for singlet, "d" for doublet, "t" for triplet, "q" for quartet, "m" for multiplet, "br" for broad, "Hz" for hertz, and "α", "β", "R", "S", "E", "Z" and "ee"

are stereochemical designations familiar to one skilled in the art.

Me
: methyl

Et
: ethyl

Pr
: propyl

i-Pr
: isopropyl

Bu
: butyl

i-Bu
: isobutyl

t-Bu
: *tert*-butyl

Ph
: phenyl

Bn
: benzyl

Hex
: hexanes

MeOH
: methanol

EtOH
: ethanol

i-PrOH or IPA
: isopropanol

AcOH or HOAc
: acetic acid

Ag_2CO_3
: silver carbonate

AgOAc
: silver acetate

$CDCl_3$
: deutero-chloroform

$CHCl_3$
: chloroform

cDNA
: complimentary DNA

DCC
: *N*,*N*'-dicyclohexylcarbodiimide

DIAD
: diisopropyl azodicarboxylate

DMA
: dimethylamine

DME
: dimethylether

DMF
: dimethyl formamide

DMSO
: dimethyl sulfoxide

DMAP
: 4-dimethylaminopyridine

EDTA
: ethylenediaminetetraacetic acid

EtOAc
: ethyl acetate

Et_2O
: diethyl ether

$AlCl_3$
: aluminum chloride

Boc
: *tert*-butyloxycarbonyl

CH_2Cl_2
: dichloromethane

CH_3CN or ACN
: acetonitrile

CS_2CO_3
: cesium carbonate

HCl
: hydrochloric acid

H_2SO_4
: sulfuric acid

K_2CO_3
: potassium carbonate

KCN
: potassium cyanide

mCPBA or m-CPBA
: *meta*-chloroperbenzoic acid

Pd/C
: palladium on carbon

$PhSO_2Cl$
: benzenesulfonyl chloride

i-Pr_2NEt
: diisopropylethylamine

PS
: polystyrene

SFC
: Supercritical Fluid Chromatography

SiO_2
: silica oxide

$SnCl_2$
: tin(II) chloride

TBAT
: tetrabutylammonium triphenydifluorosilicate

TEA
: triethylamine

TFA
: trifluoroacetic acid

THF
: tetrahydrofuran

KOAc
: potassium acetate

$MgSO_4$
: magnesium sulfate

NaCl
: sodium chloride

NaH
: sodium hydride

$NaHCO_3$
: sodium bicarbonate

NaOH
: sodium hydroxide

Na_2SO_3
: sodium sulfite

Na_2SO_4
: sodium sulfate

NH_3
: ammonia

NH_4Cl
: ammonium chloride

NH_4OH
: ammonium hydroxide

LG
: leaving group

Pd_2dba_3
: tris(dibenzylideneacetone)dipalladium(0)

selectFluor
: *N*-fluoro-*N*,'-methyl-triethylenediamine bis(tetrafluoroborate)

[0193] The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent or solvent mixture appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention.

[0194] The novel compounds of this invention may be prepared using the reactions and techniques described in this section. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. Restrictions to the substituents that are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

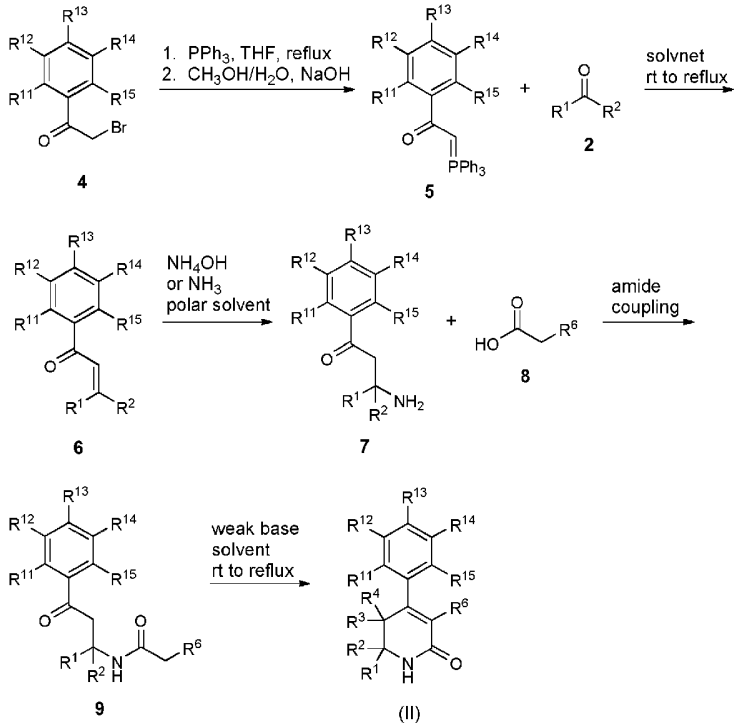
SYNTHESIS

[0195] The compounds of Formula (I) may be prepared by the exemplary processes described in the following schemes and working examples, as well as relevant published literature procedures that are used by one skilled in the art. Exemplary reagents and procedures for these reactions appear hereinafter and in the working examples. Protection and de-protection in the processes below may be carried out by procedures generally known in the art (see, for example, Wuts, P. G. M. and Greene, T.W. Protecting Groups in Organic Synthesis, 4th Edition, Wiley (2007)). General methods of organic synthesis and functional group transformations are found in: Trost, B.M. and Fleming, I., eds., Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry, Pergamon Press, New York, NY (1991); Smith, M. B. and March, J., March's Advanced Organic Chemistry: Reactions, Mechanism, and Structure. 6th Edition, Wiley & Sons, New York, NY (2007); Katritzky, A.R. and Taylor, R. J. K., eds., Comprehensive Organic Functional Groups Transformations II, 2nd Edition, Elsevier Science Inc., Tarrytown, NY (2004); Larock, R.C., Comprehensive Organic Transformations, VCH Publishers, Inc., New York, NY (1999), and references therein.

[0196] For example, compounds of Formula (II), where $R^3 = R^4 = H$, may be made according to Scheme 2. α-Bromoketone **4** is combined with triphenylphosphine in a solvent such as THF, CH_2Cl_2 or 1,4-dioxane at temperatures between room temperature and reflux. The intermediate triphenylphosphonium bromide is treated with base, such as NaOH, in a solvent such as methanol and water to form the phosphorous ylide **5.** The phosphorous ylide **5** is heated to 80 °C with ketone **2** in a suitable solvent such as THF or DMSO to give α,β-unsat'd ketone **6,** which may exist as a mixture of E/Z isomers. Microwave irradiation may be employed to shorten the reaction time. α,β-Unsat'd ketone **6** is treated with concentrated aq NH_4OH in a solvent such as DMSO in

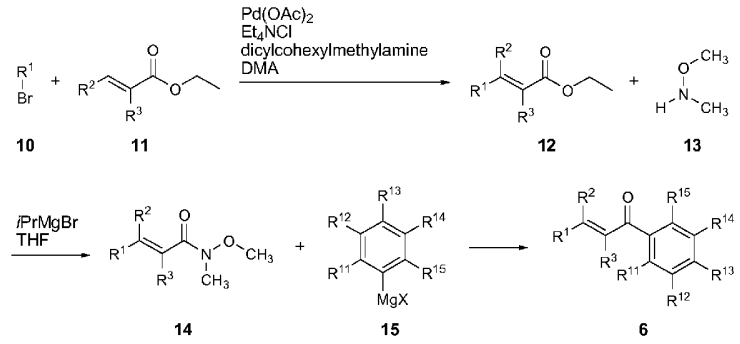
a sealed vessel to provide amine 7. Alternatively, alkene **6** may be treated with NH_3 in a solvent such as DMSO or DMSO and methanol in a sealed vessel to provide amine **7.** Amine **7** is couple with carboxylic acid **8** using a variety of amide bond forming reactions. For example, carboxylic acid **8** may be converted to the corresponding acid chloride using oxalyl chloride in a solvent such as CH_2Cl_2 and catalytic DMF. Alternatively, when R^6 is an amide or a heterocycle, the carboxylic acid **8** may be activated using triphenylphosphine and trichloroacetonitrile in a suitable solvent such as CH_2Cl_2. The acid chlorides thus formed are combined with amine **7** in a suitable solvent such as CH_2Cl_2 or CH_2Cl_2 and DMF in the presence of a base, preferably pyridine. When R^2 is CF_3, cyclization of amide **9** to a compound of Formula (I) typically occurs during the work-up procedure for amide **9;** for example, when an EtOAc solution of amide **9** is washed with sat'd aq $NaHCO_3$. When cyclization does not occur under these conditions, cyclization may be affected by stirring amide **9** in the presence of a weak base such as piperidine in a suitable solvent such as EtOH at a temperature between room temperature and reflux.

Scheme 2



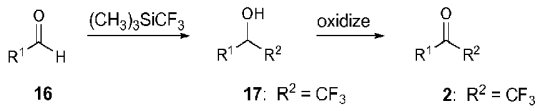
[0197] An alternate synthesis to α,β-unsaturated ketone **6,** where R^1 is $-(CH_2)_m-$ (phenyl substituted with 0-2 R^b) and m = 0, is shown in Scheme 3. Aryl bromide **10** and α,β-unsat'd ester **11** are coupled using palladium (II) acetate, tetrabutylammonium chloride and dicyclohexylamine in DMA at 110 °C. α,β-Unsat'd ester **12** is combined with O,*N*-dimethylhydroxyl-amine **13** in the presence of a strong base such as *iso*-propylmagnesium bromide in an aprotic solvent such as THF. α,β-Unsat'd amide **14** is combined with aryl magnesium halide **15** to provide **-**α,β-unsat'd ketone **6.** The identity of the halide in the aryl magnesium halide is dependent upon availability of the aryl halide used to make the Grignard reagent; typically the halide is chloride or bromide.

Scheme 3



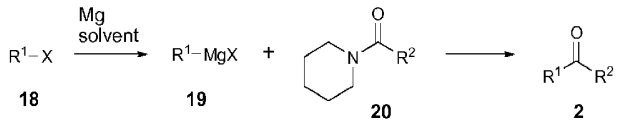
[0198] Non-commercial α,α,α-trifluoroketones **2,** where $R^2 = CF_3$, may be made from the corresponding aldehyde **16** as shown in Scheme 4. Aldehyde **16** is reacted with trimethyl-(trifluoromethyl)silane in the presence of a fluoride source, for example cesium fluoride, using a suitable solvent such dimethoxyethane at room temperature. Other fluoride sources, such as potassium hydrogen fluoride or tetrabutylammonium difluorotriphenylsilicate, and other solvents, such as THF or acetonitrile and methanol, may also be employed. Trifluoromethyl alcohol **17** is oxidized using, for example, Dess-Martin periodinane in a suitable solvent such as CH_2Cl_2.

Scheme 4



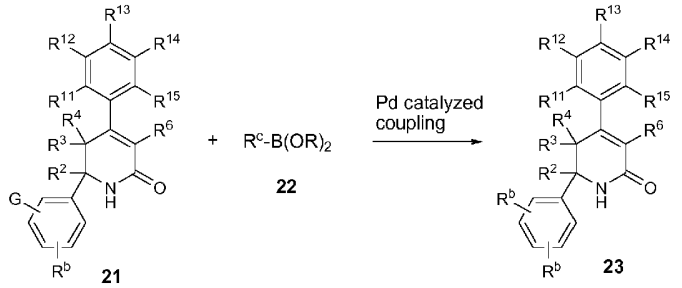
[0199] Ketones of formula **2** may be made according to Scheme 5. For example, aryl halide **18,** where X = bromine and the aryl group is a suitable chemical moiety to form a Grignard reagent, is combined with magnesium metal in the presence of an initiator such as iodine in a suitable solvent such as THF. Other alkyl halides having a chemical moiety suitable for formation of Grignard reagents, other halides such as chlorine or iodine, other solvents such as diethyl ether or 1,4-dioxane, and other initiators such as 1,2-dibromoethene, may be employed as determined by one skilled in the art. Grignard reagent **19** is combined with amide **20** in a suitable solvent such as THF to provide ketone **2.** Other solvents such as 1,4-dioxane or diethyl ether may be employed as determined by one skilled in the art.

Scheme 5



[0200] Compounds of Formula **23** having $R^3 = R^4 = H$, $R^1 = -(CH_2)_m$-(phenyl substituted with 0-2 R^b) where m = 0, and at least one $R^b = -(CH_2)_n-(X)_t-(CH_2)_m-R^c$ where n = m = t = 0, or n = m = 0 and t = 1 when X = O or NH, and R^c is a suitable chemical moiety to participate in palladium cross coupling reactions, may be made according to Scheme 6. Compound **21** is heated with boronic acid **22,** where R = H, in the presence of a palladium catalyst and base using a suitable solvent such as 1,4-dioxane, toluene, DMF with or without water. Boronic acid **22** may be substituted with alternative boronic acid analogs such as boronate esters, trifluoroborates, and others known to those skilled in the art. Palladium catalyst commonly employed include, but are not restricted to, $Pd(PPh_3)_4$ and $PdCl_2$(dppf). Other palladium catalyst known to those skilled in the art may be employed. Bases commonly employed include, but are not restricted to, K_3POP_4 and K_2CO_3. Other bases known to those skilled in the art may also be employed. When n = m = 0 and t = 1 when X = O or NH, biarylethers or biarylamines such as **23** can be obtained from **21** when G = OH. Alternatively, biaryl ethers and amines can also be obtained from **21,** when G = boronic acid or equivalent, via metal-catalyzed coupling with suitable phenols or amines.

Scheme 6

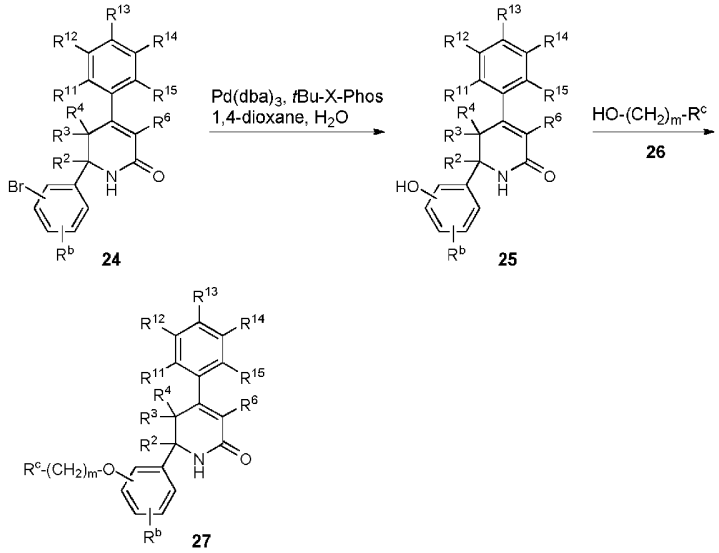


G = Cl, Br, I, OMs, OTs, OTf, OH, NH_2

[0201] Compounds of Formula **27** having $R^3 = R^4 = H$, $R^1 = -(CH_2)_m$-(phenyl substituted with 0-2 R^b) where m = 0, and at least one $R^b = -(CH_2)_n-(X)_t-(CH_2)_m-R^c$ where n = 0, t = 1, m = 1-4 and X = O, may be made according to Scheme 7. Bromide **24** is treated with tris(dibenzylideneacetone)palladium (0) in the presence of bis(1,1-dimethylethyl)[2',4',6'-tris(1-methylethyl)[1,1'-

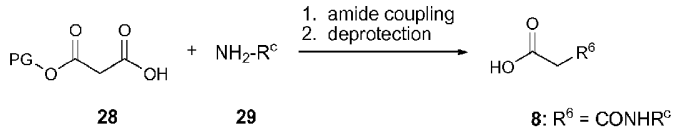
biphenyl]-2-yl]- phosphine (*t*-butyl-Xphos) using 1,4-dioxane and water as solvent and KOH as base. Phenol **25** and alcohol **26** were stirred in the presence of triphenylphosphine and DIAD in a suitable solvent such as CH_2Cl_2.

Scheme 7



[0202] Carboxylic acid **8,** where R^6 = $CONHR^c$, may be made according to Scheme 8. The mono-ester of malonic acid **28,** where PG = benzyl group, and amine **29** are coupled together using standard amide bond forming conditions. For example, treatment of carboxylic acid **28** with oxalyl chloride in CH_2Cl_2 and DMF provides the acid chloride. The acid chloride is then combined with amine **29** in the presence of pyridine in a suitable solvent such as CH_2Cl_2. Other amide bond forming reaction known to those skilled in the art may be employed. The benzyl group is removed using a combination of hydrogen gas and 10% palladium on carbon in a suitable solvent such as methanol or methanol and EtOAc. Other PG moieties and methods for their removal known to those skilled in the art may be employed.

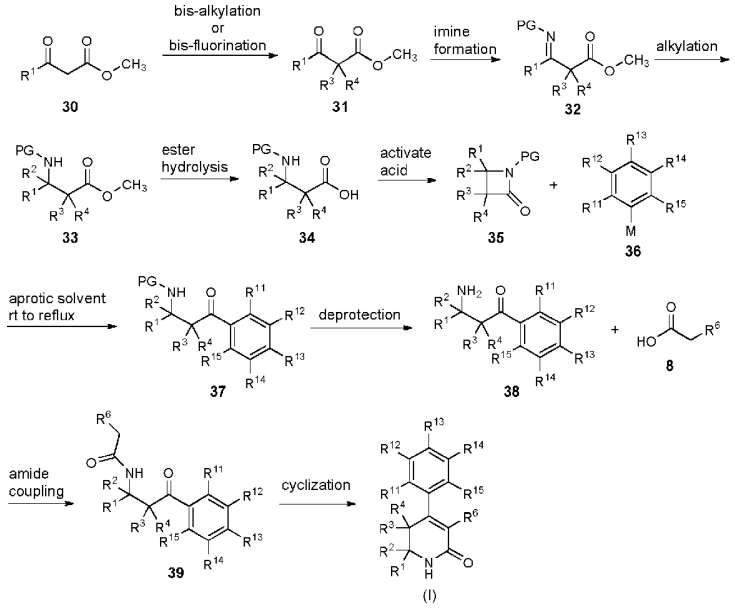
Scheme 8



[0203] Compounds of Formula (I), where R^3 and R^4 are combined with the carbon atom to which they are attached to form a 3-6 membered carbocycle, or R^3 = R^4 = F, may be made according to Scheme 9. For example, to synthesize compounds for Formula (I) where R^3 and R^4 are combined with the carbon atom to which they are attached to form a 3-membered ring (*i.e.*, cyclopropyl), β-ketoester **30** is stirred at room temperature with 1,2-dibromoethane in the presence of a base, for example K_2CO_3, in a suitable solvent such as DMF to provide the cyclopropyl β-ketoester **31.** Cyclopropyl β-ketoester **31** is stirred with a suitable amine, such as benzyl amine, in the presence of a suitable Lewis acid, such as $TiCl_4$, in a solvent such as CH_2Cl_2 starting at 0 °C then warming to room temperature. Other amines, Lewis acids, solvents and temperatures may be used as determined by those skilled in the art. The use of benzylamine provides imine **32,** where PG = benzyl. Imine **32** is alkylated with, for example, trimethyl(trifluoromethyl)silane in the presence of a fluoride source such as potassium hydrogen fluoride and TFA, using acetonitrile and DMF. Other fluoride sources, such as tetrabutylammonium difluorotriphenylsilicate or cesium fluoride, other acids such as HOAc or HCl, and other solvents may be employed as determined by those skilled in the art. Use of trimethyl(trifluoromethyl)silane provides amino ester **33,** where R^2 = CF_3. Ester hydrolysis of amino ester **33** was done in the presence of lithium iodide in refluxing pyridine to provide amino acid **34.** Use of other hydrolysis conditions known to those skilled in the art may be employed. Cyclization of amino acid **34** to β-lactam **35** was affected by activating the carboxylic acid of amino acid **34** with oxalyl chloride in a suitable solvent such as CH_2Cl_2 containing catalytic DMF. The cyclization occurred spontaneously at room temperature to provide β-lactam **35.** Other methods for activating the carboxylic acid may be employed as determined by those skilled in the art. β-Lactam **35** is arylated using an organometallic reagent. Organometallic reagents may include, for example, Grignard reagents or organolithium reagents, formed from a suitably substituted phenyl ring containing a halide atom able to react with either elemental magnesium to form a Grignard reagent or with an alkyl lithium reagent to form an phenyl lithium

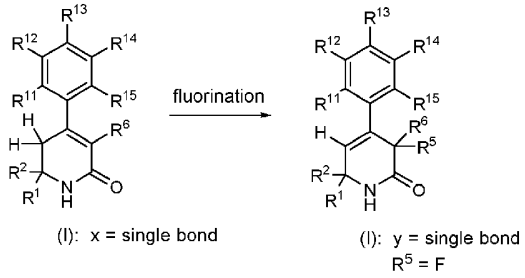
reagent via transmetallation. Exact conditions required to form these phenyl organometallic species must determined by those skilled in the art. A suitable aprotic solvent is used, for example, THF. Other suitable solvents may be employed as determined by those skilled in the art. The reaction is carried out between room temperature and reflux depending upon the identity of the organometallic reagent employed and the substitution pattern on β-lactam **35.** The β-amino ketone **37** thus formed is deprotected using hydrogen gas and 10% palladium on carbon in a suitable solvent such as methanol containing 4.4% formic acid to provide β-amino ketone **38.** Other conditions to remove the benzyl group may be employed as determined by those skilled in the art. β-Amino ketone **38** is acylated with carboxylic acid **8** using conditions described in Scheme 2 to give the β-keto amide **39.** Stirring β-keto amide **39** with a base such as sodium ethoxide in a suitable solvent such as ethanol at room temperature provides compounds having Formula (I).

Scheme 9



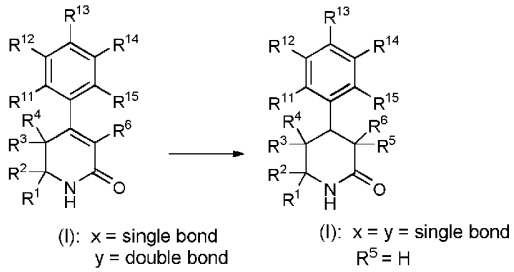
[0204] Compounds of Formula (I), where y is a single bond and R^5 = F may be made according to Scheme 10.

Scheme 10



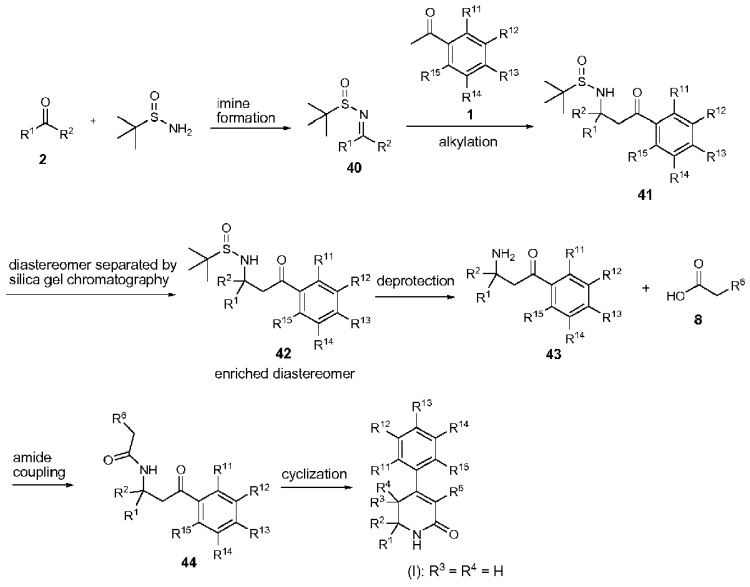
[0205] Compounds of Formula (I), where x and y are both single bonds and R^5 = H, can be made according to Scheme 11. Reduction of compounds of Formula (I), where x equals a single bond and y equals a double bond, is carried out using a suitable catalyst such as palladium on carbon under an atmosphere of hydrogen gas at suitable pressure, such as 50 psi, to effect reduction of the double bond y to a single bond. Suitable solvents include, but are not restricted to, methanol.

Scheme 11



[0206] Compounds of Formula (II), single enantiomer, where $R^3 = R^4$ =H, can be it made according to Scheme 12. Ketone **2** was stirred with 2-methylpropane-2-sulfinamide in the presence of a suitable Lewis acid, such as $Ti(OEt)_4$, in a solvent such as THF at refluxed tempereature provides imine **40.** Other Lewis acids, solvents and temperatures may be used as determined by those skilled in the art. Imine **40** is alkylated with ketone **1** in the presence of a base, such as LiHMDS, KHMDS, NaHMDS, or LDA in an aprotic solvent such as THF or ether at a temperature ranging from -78 °C to ambient to provide β-amino ketone **41** as a mixture of two diastereomers, which can be separated by silica gel chromatography to give the desired isomer **42.** Other metal enolates (such as titanium enolate), solvents, and temperatures may be used as determined by those skilled in the art (T. P. Tang, J. A Ellman, J. Org. Chem. 1999, 64, 12-13, J. Org. Chem. 2002, 67, 7819-7832). Preferably, chiral *S*- or *R*-2-methylpropane-2-sulfinamide can be optionally used to generate each of the optically pure enantiomers of imine **40** that can allow for chiral induction to prepare diastereomerically enriched ketone **42.** In these cases, the product mixture can be further purified by silica gel chromatography to obtain desired products with diaseteromeric excess of >97%. β-amino ketone 42 thus formed is deprotected using HCl in a suitable solvent such as MeOH to provide β-amino ketone **43.** Other conditions to remove the *t*-butylsulfinyl group may be employed as determined by those skilled in the art. β-amino ketone **43** is acylated with carboxylic acid **8** using conditions described in Scheme 2 to give the β-keto amide **44.** Stirring β-keto amide **44** with a base such as sodium ethoxide in a suitable solvent such as ethanol at room temperature provides compounds having Formula (II).

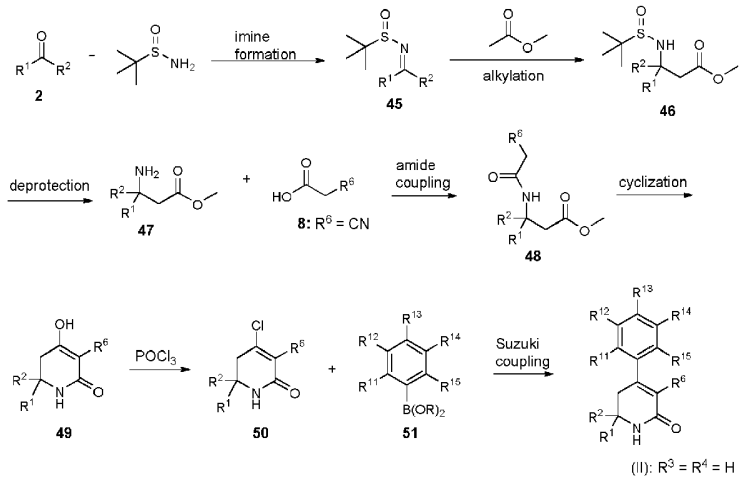
Scheme 12



[0207] Alternatively, compounds of Formula (II), where $R^3 = R^4$ =H, may be made according to Scheme 13. Ketone **2** can be reacted with 2-methylpropane-2-sulfinamide in the presence of a suitable Lewis acid, such as $Ti(OEt)_4$, in a solvent such as THF at a temperature ranging from ambient to reflux to provide imine **45.** Other Lewis acids, solvents and temperatures may be used as determined by those skilled in the art. Imine **45** is alkylated with the enolate of an ester in a suitable aprotic solvent such as THF or ether starting at -78 °C then warming to 0 °C or room temperature to provide protected β-amino ketone **46** as a mixture of two diastereomers, which can be separated by silica gel chromatography to give each individual chiral compound. The generation of the ester enolate is achieved by treating the ester, such as methyl acetate, with a suitable base such as LHMDS, KHMDS, NaHMDS, or LDA in an aprotic solvent such as THF or ether at a temperature ranging from -78 °C to ambient. Other metal enolates (such as titanium enolate), solvents, and temperatures may be used as determined by those skilled in the art (T. P.

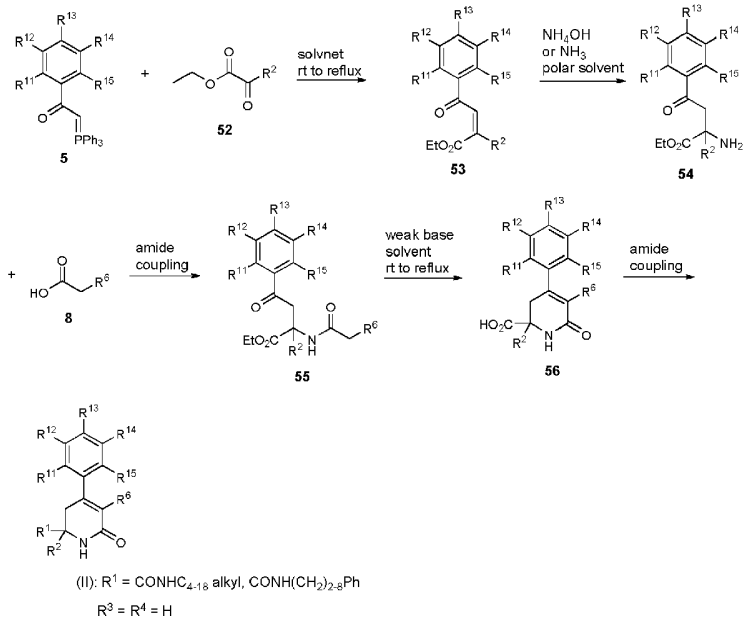
Tang, J. A Ellman, J. Org. Chem. 1999, 64, 12-13 , J. Org. Chem. 2002, 67, 7819-7832). Preferably, chiral *S*- or *R*-2-methylpropane-2-sulfinamide can be optionally used to generate each of the optically pure enantiomers of imine **45** that can allow for chiral induction to prepare diastereomerically enriched ester **46.** In these cases, the product mixture can be further purified by silica gel chromatography to obtain desired products with diaseteromeric excess of >97%. The tert-butyl sulfinyl group of **46** is removed using acids such as HCl and TFA in a suitable solvent such as MeOH or dioxane to generate amino ester **47.** Other conditions to remove the *t*-butylsulfinyl group may be employed as determined by those skilled in the art. β-Amino ketone **47** is acylated with carboxylic acid **8** using conditions described in Scheme 2 to give the β-keto amide **48.** Stirring β-keto amide **48** with a base such as sodium ethoxide in a suitable solvent such as ethanol at room temperature to 80°C provides cyclic enol **49.** Other conditions can also by used to effect the cyclization as determined by those skilled in the art. Compound **49,** when treated with stoichiometric amount of a chlorinating agent, such as $POCl_3$, at elevated temperature in an inert solvent such as toluene, is converted to mono-chloride **50.** Chloride **50** can then react with various boronic reagents through a Suzuki-type of cross coupling reaction to generate compounds of Formula (II). The choices of boronic reagents, catalysts, ligands, bases, solvents and temperatures are well documented in the literature and can be selected appropriately by those skilled in the art.

Scheme 13



[0208] Compounds of Formula (II), where $R^3 = R^4$ =H and R^1 = $CONHC_{4-18}$ alkyl or $CONH(CH_2)_{1-8}Ph$ can be made according to Scheme 14. The phosphorous ylide **5** is heated, using microwave irradiation, to 150 °C with α-ketoester **52** in a suitable solvent such as THF or DMSO to give α,β-unsat'd ketone **53.** α,β-Unsat'd ketone **53** is treated with concentrated aq NH_4OH in a solvent such as DMSO in a sealed vessel to provide amine **54.** Alternatively, alkene **53** may be treated with NH_3 in a solvent such as DMSO or DMSO and methanol in a sealed vessel to provide amine **54.** Amine **54** is couple with carboxylic acid **8** using a variety of amide bond forming reactions. For example, carboxylic acid **8** may be converted to the corresponding acid chloride using oxalyl chloride in a solvent such as CH_2Cl_2 and catalytic DMF. Alternatively, the carboxylic acid **8** may be activated using 1-chloro-N,N,2-trimethylprop-en-1-amine in a suitable solvent such as CH_2Cl_2. The acid chlorides thus formed are combined with amine **54** in a suitable solvent such as CH_2Cl_2 or CH_2Cl_2 and DMF in the presence of a base, preferably pyridine. Other amide bond forming reaction known to those skilled in the art may be employed. Cyclization of amide **55** and susequent hydrolysis to a the carboxylic acid **56** typically occurs by stirring amide **55** in the presence of a weak base such as piperidine in a suitable solvent such as EtOH at a temperature between room temperature and reflux or a base such as litium hydroxide in a suitable solvent such as THF and water at room temperature. Hydrolysis is then carried out under acidic conditions using a strong acid such as HCl in a suitable solvent such as acetic acid at temperatures between room temperature and 50 °C. Carboxylic acid **56** and an amine are coupled together using standard amide bond forming conditions. For example, treatment of carboxylic acid **56** and an amine with HOBt, EDC and DIEA in the presence of pyridine in a suitable solvent such as DCM at room temperature provides compounds having Formula (II). Other amide bond forming reaction known to those skilled in the art may be employed.

Scheme 14



IV. BIOLOGY

[0209] In mammals, there are two triglyceride synthesis pathways: glycerol-3-phosphate pathway and monoacylglycerol pathway. The former is mainly responsible for energy storage in the peripheral tissues such as fat, liver, skeletal muscle; the latter is essential for the dietary fat absorption which takes place in the small intestine. When dietary fat is ingested, pancreatic lipase digests triglycerides into free fatty acids and 2-monoacylglycerol, which are absorbed by intestinal epithelial enterocytes. Once inside enterocytes, free fatty acids and 2-monoacylglycerol are used as building blocks to resynthesize triglycerides by two sequential acylation steps; first by MGAT and then by DGAT enzyme reactions. Triglycerides are then incorporated into chylomicrons and secreted into lymph to be utilized as an energy supply for the body.

[0210] Monoacylglycerol acyltransferase 2 (MGAT2) is a membrane bound acyltransferase that belongs to diacylglycerol acyltransferase 2 (DGAT2) gene family. It is highly and selectively expressed in the small intestine. Genetic deletion of MGAT2 in mice decreased the rate of absorption for the orally ingested triglycerides, indicating that MGAT2 plays an important role for the intestinal MGAT/DGAT pathway [Yen, C.L. et al, Nat. Med., 15(4):442-446 (2009); Okawa, M. et al., Biochem. Biophys. Res. Commun., 390(3):377-381 (2009)]. When chronically challenged with a high fat diet, in contrast to wild type mice that became obese, MGAT2 knockout mice resisted the impact of high-fat feeding and demonstrated with a lower body weight, less adiposity, and less hepatic fat accumulation. In contrast to hyperinsulinemic wild type mice after high-fat challenge, MGAT2 deletion normalizes the insulin level and decreased fasting glucose. In the glucose tolerance test, they also had an improved glucose excursion. Consistent with their improved glycemic profile, MGAT2 knockout mice also had an increased level of GLP1, an incretin gut hormone that profoundly impacts glucose metabolism[Yen, C.L. et al., Nat. Med., 15(4):442-446 (2009)]. Taken together, it is expected that inhibition of MGAT2 through pharmacological intervention would provide the same benefit as demonstrated in the knock-out mice, e.g., resistance to weight gain, or conversely, reduction in fat body mass. In addition, MGAT2 inhibition would lead to an improved insulin sensitivity and glucose metabolism which either leads to a decrease in the incidence of Type II diabetes, or a treatment of diabetic condition.

[0211] It is also desirable and preferable to find compounds with advantageous and improved characteristics compared with known anti-diabetic agents, in one or more of the following categories that are given as examples, and are not intended to be limiting: (a) pharmacokinetic properties, including oral bioavailability, half life, and clearance; (b) pharmaceutical properties; (c) dosage requirements; (d) factors that decrease blood drug concentration peak-to-trough characteristics; (e) factors that increase the concentration of active drug at the receptor; (f) factors that decrease the liability for clinical drug-drug interactions; (g) factors that decrease the potential for adverse side-effects, including selectivity versus other biological targets; and (h) improved therapeutic index with less propensity for hypoglycemia.

[0212] As used herein, the term "patient" encompasses all mammalian species.

[0213] As used herein, the term "subject" refers to any human or non-human organism that could potentially benefit from treatment with a MGAT2 inhibitor. Exemplary subjects include human beings of any age with risk factors for metabolic disease. Common risk factors include, but are not limited to, age, sex, weight, family history, or signs of insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome (PCOS).

[0214] As used herein, "treating" or "treatment" cover the treatment of a disease-state in a mammal, particularly in a human, and include: (a) inhibiting the disease-state, *i.e.*, arresting it development; and/or (b) relieving the disease-state, *i.e.*, causing regression of the disease state.

[0215] As used herein, "prophylaxis" or "prevention" cover the preventive treatment of a subclinical disease-state in a mammal, particularly in a human, aimed at reducing the probability of the occurrence of a clinical disease-state. Patients are selected for preventative therapy based on factors that are known to increase risk of suffering a clinical disease state compared to the general population. "Prophylaxis" therapies can be divided into (a) primary prevention and (b) secondary prevention. Primary prevention is defined as treatment in a subject that has not yet presented with a clinical disease state, whereas secondary prevention is defined as preventing a second occurrence of the same or similar clinical disease state.

[0216] As used herein, "risk reduction" covers therapies that lower the incidence of development of a clinical disease state. As such, primary and secondary prevention therapies are examples of risk reduction.

[0217] "Therapeutically effective amount" is intended to include an amount of a compound of the present invention that is effective when administered alone or in combination to inhibit MGAT2 and/or to prevent or treat the disorders listed herein. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the preventive or therapeutic effect, whether administered in combination, serially, or simultaneously.

A. ASSAY METHODS

MGAT SPA Assay

[0218] MGAT2 enzyme was assayed using membranes isolated from Sf9 cells expressing the recombinant human MGAT2 cDNA with 2-monooleoylglycerol and [^{3}H]-oleoyl-CoA as substrates as described by Seethala et al. [Anal. Biochem., 383(2):144-150 (Dec. 15, 2008)]. Briefly, the assays were conducted in 384-well plates in a total volume of 30 µL at 25 °C. In each assay, 200 ng of recombinant human MGAT2 membrane was incubated with 10 µM of 2-monooleoylglycerol and 15 µM of [^{3}H]-oleoyl-CoA in 100 mM potassium phosphate (pH 7.4) for 20 min with various concentrations of compounds delivered in DMSO. The assay was terminated by the addition of 20 µl of Stopping Solution (7.5 mg/ml Yittrium Oxide Polylysine beads, 3.3 mg/ml Fraction V BSA and 200 µM Mercuric chloride in 50 mM HEPES, pH 7.4). The signal was measured 1 h after quenching the reaction using LEADSEEKER^{SM} for 5 minutes. To calculate the degree of inhibition, the zero level of enzyme activity (blank) was defined by the above assay procedure using membrane form Sf9 cell uninfected with baculovirus (Naive) and the 100% level of MGAT2 enzyme activity was defined by human MGAT2 assay with the vehicle DMSO. The IC_{50}s of inhibitors were determined by logistic 4 parameter equation in XL-fit.

MGAT LCMS Assay

[0219] The MGAT enzyme reactions were performed in CORNING® Falcon 96-well Polypropylene plates, in a total volume of 60 µL of 50 mM Potassium Phosphate buffer pH 7.4, containing a final concentration of 100 µM 2-oleoylglycerol, 15 µM oleoyl-Coenzyme A and 0.0013 µg/gL Human or Mouse MGAT-2 or 0.0026 µg/µL Rat recombinant MGAT-2 membranes expressed in Sf9 cells. Assay plates were run through a fully automated robotics system and shaken for 5 seconds every minute for a total 10 minutes. The reactions were then quenched with 120 µL of ice cold methanol containing 1 µg/mL 1,2-distearoyl-*rac*-glycerol as the internal standard. Plates were shaken for 2 minutes and spun down to remove protein precipitation. After the spin, samples were transferred to LC/MS compatible PCR plates. For LC/MS analysis, a ThermoFisher Surveyor pump, utilizing a Waters Symmetry C8, 50 x 2.1 mm column, was used for the chromatography of enzyme products. The buffer system consists of 0.1% formic acid in water with a mobile phase consisting 0.1% formic acid in methanol. The shallow gradient is 90-100% mobile phase

in 0.2 min with a total run time of 2.3 min. The first 0.5 minutes of each injection was diverted to waste to eliminate the presence of Phosphate buffer in the enzymatic reaction. The column was run at 0.6 mL/min and a temperature of 65 °C. Mass spectrometry analysis of the samples was performed on a ThermoFisher Quantum Triple quad utilizing APCI (+) as the mode of ionization. Data was acquired in Single Ion Monitoring (SIM) mode analyzing Diolein =*m/z* 603.6 (PRODUCT) and 1,2- distearoyl-*rac*-glycerol (IS)= *m/z* 607.6. The ratio of Diolein to internal standard (Peak Area Ratio) is utilized to calculate IC_{50} values.

[0220] The exemplified Examples disclosed below were tested in the MGAT2 *in vitro* assays described above and were found having MGAT2 inhibitory activity. Table 1 below lists human MGAT2 IC_{50} values measured for the following examples. "NT" denotes "Not tested".

Table 1

Example No.	h-MGAT2 IC_{50} (nM)	
	SPA Assay	LCMS Assay
2	85	5
2-1	35	8
2-2	1400	261
6	15	7
6-1	1435	NT
6-2	14	2
8	NT	7
9	33330	121
10	2716	138
11	48	13
12	NT	374
13	3333	35
16-1	25	7
16-2	8430	416
21	913	NT
38	2143	NT
41	170	15
48	226	7
49	127	64
50	242	95
51	63	13
52	477	99
54	258	20
55	846	20
56	6550	NA
57	412	16
58	275	29
59	53	4
60	441	12
61	709	NT
62	156	24
70	3404	NA
82	133	2
83	89	1

Example No.	h-MGAT2 IC_{50} (nM)	
	SPA Assay	LCMS Assay
84	115	2
85	1465	7
86	201	1
87	NT	1215
88	28	5
90	815	18
92	NT	136
93	37	30
94	32	4
95	95	43
96	NT	1431
97	NT	1199
98	154	69
99	NT	795
100	NT	1575
101	379	108
102	NT	1088
103	NT	645
104	NT	103
105	672	24
106	NT	552
110	11	5
111	9	7
112	1297	204
113	158	8
114	NT	704
115	NT	40
116	48	4
117	22	18
118	32	4
119	94	21
120	58	6
121	231	20
122	14	1
123	743	5
124	4264	55
125	NT	282
126	1874	33
127	655	10
128	NT	328
129	NT	222
130	20	1

Example No.	h-MGAT2 IC_{50} (nM)	
	SPA Assay	LCMS Assay
131	NT	1050
132	NT	163
133	1518	127
134	NT	168
135	NT	778
136	NT	328
137	NT	252
140	NT	356
141	NT	459
142	93	10
143	156	4
148	102	9
149	53	6
150	11	3
151	NT	5115
152	NT	252
153	NT	247
154	34	8
155	NT	484
156	NT	254
157	168	84
158	302	75
159	NT	16710
161	NT	1261
162	NT	214
163	1176	47
164	NT	162
165	60	8
166	237	102
167	8	2
168	NT	113
169	NT	421
170	NT	210
171	724	57
172	16	3
173	43	63
174	237	60
175	NT	264
176	NT	3
178	47	78
179	24	2
180	36	30

Example No.	h-MGAT2 IC_{50} (nM)	
	SPA Assay	LCMS Assay
181	NT	2049
182	NT	2049
183	NT	50
185	NT	121
186	NT	229
187	NT	4
188	NT	1524
189	NT	1159
190	NT	155
191	NT	797
192	NT	433
193	NT	46
194	NT	6
195	NT	33
196	NT	826
197	NT	178
198	NT	16
199	NT	16
200	NT	37
201	NT	24
202	NT	89
203	NT	59
204	NT	41
205	NT	13
206	NT	78
207	NT	11
208	NT	30
209	NT	37
210	NT	2
211	NT	97
212	NT	416
213	NT	1096
214	NT	12
228	NT	7
229	NT	25
231	NT	34
232	NT	6
233	NT	639
234	NT	40
235	NT	22
236	NT	489
237	NT	130

Example No.	h-MGAT2 IC_{50} (nM)	
	SPA Assay	LCMS Assay
238	NT	7
239	NT	15
240	NT	7
242	NT	44
243	NT	14
244	NT	61
245	NT	46
246	NT	36
247	NT	51
248	NT	8
249	NT	185
250	NT	243
251	NT	3
252	NT	7
253	NT	411
254	NT	170
255	NT	702
265	NT	40
266	NT	10
267	NT	796
268	NT	8
270	NT	407
271	NT	12
272	NT	112
273	21	10
274	NT	1
275	NT	2
276	NT	2
277	NT	2
278	NT	2
279	NT	2
280	NT	2
281	NT	3
282	NT	3
283	NT	3
284	NT	4
285	NT	4
286	NT	4
287	NT	13
288	NT	19
289	NT	19
290	NT	56

Example No.	h-MGAT2 IC_{50} (nM)	
	SPA Assay	LCMS Assay
291	NT	178
292	NT	304
293	NT	7
294	NT	84
295	NT	183
296	NT	2
297	NT	639
298	NT	2
299	NT	11
300	NT	11
301	NT	19
302	NT	105
303	NT	28
304	NT	6
305	NT	94
306	NT	3
307	NT	3
308	NT	61
309	NT	1
310	NT	4
311	NT	3
312	NT	21
313	NT	4
314	NT	109

[0221] The compounds of the present invention possess activity as inhibitors of MGAT2, and, therefore, may be used in the treatment of diseases associated with MGAT2 activity. Via modulation of MGAT2, the compounds of the present invention may preferably be employed to modulate, either enhance or decrease the production/secretion of insulin and/or gut hormones, such as GLP1, GIP, CCK, PYY, PP, Amylin.

[0222] Accordingly, the compounds of the present invention can be administered to mammals, preferably humans, for the treatment of a variety of conditions and disorders, including, but not limited to, treating, preventing, or slowing the progression of diabetes and related conditions, microvascular complications associated with diabetes, macrovascular complications associated with diabetes, cardiovascular diseases, Metabolic Syndrome and its component conditions, inflammatory diseases and other maladies. Consequently, it is believed that the compounds of the present invention may be used in preventing, inhibiting, or treating diabetes, hyperglycemia, impaired glucose tolerance, gestational diabetes, insulin resistance, hyperinsulinemia, retinopathy, neuropathy, nephropathy, wound healing, atherosclerosis and its sequelae (acute coronary syndrome, myocardial infarction, angina pectoris, peripheral vascular disease, intermittent claudication, myocardial ischemia, stroke, heart failure), Metabolic Syndrome, hypertension, obesity, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL, high LDL, lipid disorders, PCOS, and glaucoma.

[0223] Metabolic Syndrome or "Syndrome X" is described in Ford et al., J. Am. Med. Assoc., 287:356-359 (2002) and Arbeeny et al., Curr. Med. Chem. - Imm., Endoc. & Metab. Agents, 1:1-24 (2001).

V. PHARMACEUTICAL COMPOSITIONS, FORMULATIONS AND COMBINATIONS

[0224] The compounds of this invention can be administered for any of the uses described herein by any suitable means, for example, orally, such as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixirs, tinctures, suspensions (including nanosuspensions, microsuspensions, spray-dried dispersions), syrups, and emulsions; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection, or infusion techniques (*e.g.,* as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

[0225] The term "pharmaceutical composition" means a composition comprising a compound of the invention in combination with at least one additional pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier" refers to media generally accepted in the art for the delivery of biologically active agents to animals, in particular, mammals, including, *i.e.*, adjuvant, excipient or vehicle, such as diluents, preserving agents, fillers, flow regulating agents, disintegrating agents, wetting agents, emulsifying agents, suspending agents, sweetening agents, flavoring agents, perfuming agents, antibacterial agents, antifungal agents, lubricating agents and dispensing agents, depending on the nature of the mode of administration and dosage forms.

[0226] Pharmaceutically acceptable carriers are formulated according to a number of factors well within the purview of those of ordinary skill in the art. These include, without limitation: the type and nature of the active agent being formulated; the subject to which the agent-containing composition is to be administered; the intended route of administration of the composition; and the therapeutic indication being targeted. Pharmaceutically acceptable carriers include both aqueous and non-aqueous liquid media, as well as a variety of solid and semi-solid dosage forms. Such carriers can include a number of different ingredients and additives in addition to the active agent, such additional ingredients being included in the formulation for a variety of reasons, e.g., stabilization of the active agent, binders, etc., well known to those of ordinary skill in the art. Descriptions of suitable pharmaceutically acceptable carriers, and factors involved in their selection, are found in a variety of readily available sources such as, for example, Allen, L. V. Jr. et al. Rernaington: The Science and Practice of Pharmacy (2 Volumes), 22nd Edition (2012), Pharmaceutical Press.

[0227] The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired.

[0228] By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to about 5000 mg per day, preferably between about 0.01 to about 1000 mg per day, and most preferably between about 0.1 to about 250 mg per day. Intravenously, the most preferred doses will range from about 0.01 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

[0229] The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, *e.g.*, oral tablets, capsules, elixirs, and syrups, and consistent with conventional pharmaceutical practices.

[0230] Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 2000 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.1-95% by weight based on the total weight of the composition.

[0231] A typical capsule for oral administration contains at least one of the compounds of the present invention (250 mg), lactose (75 mg), and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

[0232] A typical injectable preparation is produced by aseptically placing at least one of the compounds of the present invention (250 mg) into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of physiological saline, to produce an injectable preparation.

[0233] The present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, a therapeutically effective amount of at least one of the compounds of the present invention, alone or in combination with a pharmaceutical carrier. Optionally, compounds of the present invention can be used alone, in combination with other compounds

of the invention, or in combination with one or more other therapeutic agent(s), *e.g.*, an antidiabetic agent or other pharmaceutically active material.

[0234] The compounds of the present invention may be employed in combination with other MGAT2 inhibitors or one or more other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents, antihyperglycemic agents, anti-hyperinsulinemic agents, anti-retinopathic agents, anti-neuropathic agents, anti-nephropathic agents, anti-atherosclerotic agents, anti-ischemic agents, anti-hypertensive agents, anti-obesity agents, anti-dyslipidemic agents, anti-dyslipidemic agents, anti-hyperlipidemic agents, anti-hypertriglyceridemic agents, anti-hypercholesterolemic agents, anti-restenotic agents, anti-pancreatic agents, lipid lowering agents, anorectic agents, memory enhancing agents, anti-dementia agents, or cognition promoting agents, appetite suppressants, treatments for heart failure, treatments for peripheral arterial disease and anti-inflammatory agents.

[0235] Where desired, the compound of the present invention may be used in combination with one or more other types of antidiabetic agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection. The other type of antidiabetic agent that may be optionally employed in combination with the MGAT2 inhibitor of the present invention may be one, two, three or more antidiabetic agents or antihyperglycemic agents which may be administered orally in the same dosage form, in a separate oral dosage form, or by injection to produce an additional pharmacological benefit.

[0236] The antidiabetic agents used in the combination with the compound of the present invention include, but are not limited to, insulin secretagogues or insulin sensitizers, other MGAT2 inhibitors, or other antidiabetic agents. These agents include, but are not limited to, dipeptidyl peptidase IV (DP4) inhibitors (for example, sitagliptin, saxagliptin, alogliptin, vildagliptin and the like), biguanides (for example, metformin, phenformin and the like), sulfonyl ureas (for example, glyburide, glimepiride, glipizide and the like), glucosidase inhibitors (for example, acarbose, miglitol, and the like), PPARγ agonists such as thiazolidinediones (for example, rosiglitazone, pioglitazone, and the like), PPAR α/γ dual agonists (for example, muraglitazar, tesaglitazar, aleglitazar, and the like), glucokinase activators (as described in Fyfe, M.C.T. et al., Drugs of the Future, 34(8):641-653 (2009)), GPR40 receptor modulators, GPR119 receptor modulators (MBX-2952, PSN821, APD597 and the like), SGLT2 inhibitors (dapagliflozin, canagliflozin, remagliflozin and the like), amylin analogs such as pramlintide, and/or insulin. Reviews of current and emerging therapies for the treatment of diabetes can be found in: Mohler, M.L. et al., Medicinal Research Reviews, 29(1):125-195 (2009), and Mizuno, C.S. et al., Current Medicinal Chemistry, 15:61-74 (2008).

[0237] The compounds of the present invention may also be optionally employed in combination with agents for treating complication of diabetes. These agents include PKC inhibitors and/or AGE inhibitors.

[0238] The compounds of the present invention may also be optionally employed in combination with one or more hypophagic agents such as diethylpropion, phendimetrazine, phentermine, orlistat, sibutramine, lorcaserin, pramlintide, topiramate, MCHR1 receptor antagonists, oxyntomodulin, naltrexone, Amylin peptide, NPY Y5 receptor modulators, NPY Y2 receptor modulators, NPY Y4 receptor modulators, cetilistat, 5HT2c receptor modulators, and the like. The compound of structure I may also be employed in combination with an agonist of the glucagon-like peptide-1 receptor (GLP-1 R), such as exenatide, liraglutide, GPR-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener), which may be administered via injection, intranasal, or by transdermal or buccal devices. Reviews of current and emerging therapies for the treatment of obesity can be found in: Melnikova, I. et al., Nature Reviews Drug Discovery, 5:369-370 (2006); Jones, D., Nature Reviews: Drug Discovery, 8:833-834 (2009); Obici, S., Endocrinology, 150(6):2512-2517 (2009); and Elangbam, C.S., Vet. Pathol., 46(1):10-24 (2009).

[0239] The compounds of the present invention may also be optionally employed in combination with one or more other types of therapeutic agents, such as DGAT inhibitors, LDL lowering drugs such as statins (inhibitors of HMG CoA reductase) or inhibitors of cholesterol absorption, modulators of PCSK9, drugs increase HDL such as CETP inhibitors.

[0240] The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used, for example, in those amounts indicated in the *Physicians' Desk Preference*, as in the patents set out above, or as otherwise determined by one of ordinary skill in the art.

[0241] Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of the present invention and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined

active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material that affects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a low viscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

[0242] These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

[0243] The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. By "administered in combination" or "combination therapy" it is meant that the compound of the present invention and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination, each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect.

[0244] The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the MGAT2 enzyme. Such compounds may be provided in a commercial kit, for example, for use in pharmaceutical research involving MGAT2 or anti-diabetic activity. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimentor that the assay was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

[0245] The compounds of the present invention may also be used in diagnostic assays involving MGAT2.

[0246] The present invention also encompasses an article of manufacture. As used herein, article of manufacture is intended to include, but not be limited to, kits and packages. The article of manufacture of the present invention, comprises: (a) a first container; (b) a pharmaceutical composition located within the first container, wherein the composition, comprises: a first therapeutic agent, comprising: a compound of the present invention or a pharmaceutically acceptable salt form thereof; and, (c) a package insert stating that the pharmaceutical composition can be used for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2 (as defined previously). In another embodiment, the package insert states that the pharmaceutical composition can be used in combination (as defined previously) with a second therapeutic agent for the treatment and/or prophylaxis of multiple diseases or disorders associated with MGAT2. The article of manufacture can further comprise: (d) a second container, wherein components (a) and (b) are located within the second container and component (c) is located within or outside of the second container. Located within the first and second containers means that the respective container holds the item within its boundaries.

[0247] The first container is a receptacle used to hold a pharmaceutical composition. This container can be for manufacturing, storing, shipping, and/or individual/bulk selling. First container is intended to cover a bottle, jar, vial, flask, syringe, tube *(e.g.,* for a cream preparation), or any other container used to manufacture, hold, store, or distribute a pharmaceutical product.

[0248] The second container is one used to hold the first container and, optionally, the package insert. Examples of the second container include, but are not limited to, boxes *(e.g.,* cardboard or plastic), crates, cartons, bags *(e.g.,* paper or plastic bags), pouches, and sacks. The package insert can be physically attached to the outside of the first container via tape, glue, staple, or another method of attachment, or it can rest inside the second container without any physical means of attachment to the first container. Alternatively, the package insert is located on the outside of the second container. When located on the outside of the second container, it is preferable that the package insert is physically attached via tape, glue, staple, or another method of attachment. Alternatively, it can be adjacent to or touching the outside of the second container without being physically attached.

[0249] The package insert is a label, tag, marker, etc. that recites information relating to the pharmaceutical composition located within the first container. The information recited will usually be determined by the regulatory agency governing the area in which

the article of manufacture is to be sold (*e.g.,* the United States Food and Drug Administration). Preferably, the package insert specifically recites the indications for which the pharmaceutical composition has been approved. The package insert may be made of any material on which a person can read information contained therein or thereon. Preferably, the package insert is a printable material (*e.g.*, paper, plastic, cardboard, foil, adhesive-backed paper or plastic, etc.) on which the desired information has been formed (*e.g.*, printed or applied).

[0250] Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments that are given for illustration of the invention and are not intended to be limiting thereof.

VI. EXAMPLES

[0251] The following Examples are offered as illustrative, as a partial scope and particular embodiments of the invention and are not meant to be limiting of the scope of the invention. Abbreviations and chemical symbols have their usual and customary meanings unless otherwise indicated. Unless otherwise indicated, the compounds described herein have been prepared, isolated and characterized using the schemes and other methods disclosed herein or may be prepared using the same.

HPLC/MS, PREPARATORY/ANALYTICAL HPLC, AND CHIRAL SEPARATION METHODS EMPLOYED IN CHARACTERIZATION OR PURIFICATION OF EXAMPLES

[0252] Analytical HPLC/MS (unless otherwise noted) was performed on Shimadzu SCL-10A liquid chromatographs and Waters MICROMASS® ZQ Mass Spectrometers (Desolvation Gas: Nitrogen; Desolvation Temp. 250 °C; Ion Source Temp: 120 °C; Positive Electrospray conditions) using the following methods:

Linear Gradient of 0% to 100% solvent B over 2 min, with 1 minute hold at 100% B, or

Linear Gradient of 0% to 100% solvent B over 4 min, with 1 minute hold at 100% B; UV visualization at 220 nm;

Column: PHENOMENEX® Luna C18 (2) 30mm × 4.6 mm; 5µ particle (heated to Temp. 40 °C);

Flow rate: 1.0 mL/min (2 min gradient) or 0.8 ml/min (4 min gradient);

Solvent A: 10% ACN, 90% water, 0.1 % TFA; or, 10% MeOH, 90% water, 0.1 % TFA and

Solvent B: 90% ACN, 10% water, 0.1 % TFA; or, 90% MeOH, 10% water, 0.1 % TFA.

[0253] Preparatory HPLC (unless otherwise noted) was performed on a Shimadzu SCL-10A liquid chromatograph with a linear gradient of 20-100% Solvent B over 10 to 30 min, with either a 2 to 5 min hold at 100% Solvent B as determined by on skilled in the art;
UV visualization at 220 nm;
Column: PHENOMENEX® Luna Axia 5µ C18 30 × 100 mm;
Flow rate: 20 mL/min;
Solvent A: 10% ACN, 90% water, 0.1 % TFA; or 10% MeOH, 90% water, 0.1 % TFA; and
Solvent B: 90% ACN, 10% water, 0.1 % TFA; or 90% MeOH, 10% water, 0.1 % TFA.

[0254] Preparatory chiral SFC chromatography (unless otherwise noted) was performed on a Berger Multigram II SFC chromatograph using one of the following methods:

Preparative chiral SFC method A:

Column: CHIRALCEL® OD-H, 30 × 250mm ID, 5µ

Flow rate: 90 mL/min, 100 bar BP, 40 °C

Mobile Phase: 15% Methanol /85% CO_2

Detector Wavelength: 254 nm

Injection Vol and Sample Solution: 0.5 mL of 4.65 g in 35 mL Methanol (133 mg/mL)

Preparative chiral SFC method B:

Instrument: Berger SFC MGII (HPW-2501)

Column: CHIRALPAK® IA 25 × 3 cm ID, 5 µm

Flow rate: 85.0 mL/min

Mobile Phase: 85/15/0.1,CO_2/IPA/DEA, 150 bar

Detector Wavelength: 225 nm (Lamda max)

Sample Prep and Inj. Volume: 300 µL of ~13 mg / 0.5 mL IPA (~26 mg/mL) Preparative chiral SFC method C

Column: CHIRALPAK® IA 25 × 3 cm ID, 5 µm

Flow rate: 90 mL/min

Mobile Phase: 85/15/0.1,CO_2/MeOH/DEA, 150 bar

Detector Wavelength: 270 nm (Lambda max)

Sample Prep and Inj. Volume: 300 µL of ~90 mg / 2 mL MeOH (~45 mg/mL) Preparative chiral SFC method D

Flow rate: 40 mL/min, 100 Bar, 35 °C

Mobile Phase: 20% Methanol/80% CO_2

Detector Wavelength: 224 nm (Lambda max)

Injection Volume: 300 µL

Sample Preparation: 10 mg dissolved in 0.5 mL MeCN (20 mg/mL);
17 mg dissolved in 0.5 mL MeCN (34 mg/mL)

[0255] Analytical chiral SFC chromatography (unless otherwise noted) was performed on an Aurora Analytical SFC or Berger Analytical SFC using one of the following methods:

Analytical chiral SFC method A:

Column: CHIRALCEL® OD-H, 4.6 × 250mm ID, 5 µm

Flow rate: 3.0 mL/min, 100 bar BP, 35 °C.

Mobile Phase: 15% Methanel/85% CO_2

Detector Wavelength: 220 nm

Sample Solution: 1 mg/mL in methanol (concentrated/reconstituted)

Injection Volume: 10 µL

Analytical chiral SFC method B:

Column: CHIRALPAK® IA 250 × 4.6 mm ID, 5µm

Flow rate: 2.0 mL/min

Mobile Phase: 85/15/0.1, CO_2/IPA/DEA, 150 bar

Detector Wavelength: 225 nm (Lamda max)

Injection Volume: 10 µL

Analytical chiral SFC method C:

Column: CHIRALPAK® IA 250 × 4.6 mm ID, 5 µm

Flow rate: 3.0 mL/min

Mobile Phase: 65/35/0.1, CO_2/MeOH/DEA, 150 bar

Detector Wavelength: 270 nm (Lambda max)

Injection Volume: 10 µL

Analytical chiral SFC method D:

Column: CHIRALCEL® OD, 250 × 4.6 mm ID, 10 µm

Flow rate: 2.0 mL/min, 100 bar, 35 °C

Mobile Phase: 20% Methanol/80% CO_2

Detector Wavelength: 223 nm

Injection Volume: 10 µL

NMR EMPLOYED IN CHARACTERIZATION OF EXAMPLES

[0256] ^{1}H NMR spectra (unless otherwise noted) were obtained with JEOL or Bruker FOURIER® transform spectrometers operating at 400 MHz or 500 MHz. ^{1}H-nOe experiments were performed in some cases for regiochemistry elucidation with a 400 MHz Bruker FOURIER® Transform spectrometer.

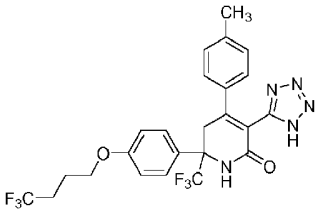
[0257] Spectral data are reported as chemical shift (multiplicity, number of hydrogens, coupling constants in Hz) and are reported in ppm (δ units) relative to either an internal standard (tetramethyl silane = 0 ppm) for ^{1}H NMR spectra, or are referenced to the residual solvent peak (2.49 ppm for CD_3SOCD_2H, 3.30 ppm for CD_2HOD, 1.94 for CHD_2CN, 7.26 ppm for $CHCl_3$, 5.32 ppm for $CDHCl_2$).

[0258] Microwave instrumentation employed in heating reactions.

[0259] BIOTAGE® Initiator 2.5, maximum power 400 W, reaction volume range 0.2 - 10 mL. Reactions are run in sealed pressure vessels specially manufactured for this instrument.

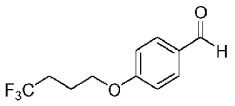
Example 2. 3-(1*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

[0260]



Intermediate 2A. 4-(4,4,4-Trifluorobutoxy)benzaldehyde

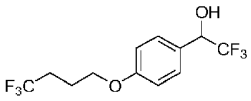
[0261]



[0262] To a solution of 4-hydroxybenzaldehyde (20 g, 164 mmol) and 4,4,4-trifluorobutan-1-ol (25 g, 195 mmol) in anhydrous CH_2Cl_2 (500 mL) at 0 °C under Ar was added a solution of PPh_3 (51.5 g, 196 mmol) in CH_2Cl_2 (200 mL) over 15 min, and then DIAD (36.4 g, 180 mmol) in anhydrous CH_2Cl_2 (150 mL) was added dropwise. The mixture was stirred at 0 °C for 0.5 h. The reaction was warmed to rt and stirred for another 3 h. The solvent was removed *in vacuo* and the residue was triturated with CH_2Cl_2 three times to remove insoluble solids. The combined CH_2Cl_2 washings were concentrated and the residue was purified by silica gel chromatography (330 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 2A (27 g, 71 %) as a light brown oil. LCMS Anal. Calc'd for $C_{11}H_{11}F_3O_2$ 232.20, found [M+H] 233.0.

Intermediate 2B. 2,2,2-Trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethanol

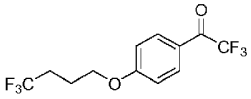
[0263]



[0264] To the solution of Intermediate 2A (26.7 g, 114 mmol) and trimethyl(trifluoromethyl)silane (16.9 g, 119 mmol) in anhydrous DME (112 mL) was added CsF (500 mg, 3.29 mmol). The reaction was stirred at rt for 16 h. To the mixture was added 4 N aq HCl (114 mL) and the reaction was stirred at rt for 2.5 h. The reaction was diluted with EtOAc (300 mL) and washed with water, sat'd aq $NaHCO_3$, sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated to provide Intermediate 2B (42.5 g, 122%) as an oil. The crude product was used without further purification. LCMS Anal. Calc'd for $C_{12}H_{12}F_6O_2$ 302.21, found [M-H] 301.2.

Intermediate 2C. 2,2,2-Trifluoro-1-(4-(4,4,4-trifluorobutoxy)phenyl)ethanone

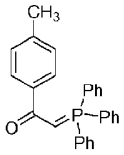
[0265]



[0266] To a solution of Intermediate 2B (115 mmol) in anhydrous CH_2Cl_2 (320 mL) was added Dess-Martin periodinane (50.2 g, 118 mmol) portionwise at 0 °C. The reaction was stirred at 0 °C for 0.5 h then at rt for 3 h. To the reaction was added 100 mL of sat'd aq Na_2CO_3 and 250 mL of EtOAc. The reaction was stirred for another 2 h. The insoluble material was removed by filtration. The layers were separated. The organic layer was washed with sat'd aq Na_2CO_3. Additional solids that formed upon standing overnight were removed. The organic solution was washed with sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated to provide a dark brown liquid, which was purified by silica gel chromatography (220 g silica gel, elute with EtOAc in hexanes to provide Intermediate 2C (26 g, 76%) as a colorless oil.

Intermediate 2D. Triphenylphosphonium *p*-tolylcarbonylylide

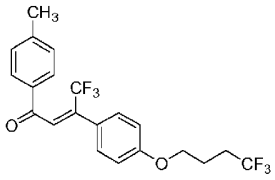
[0267]



[0268] To a refluxing solution of PPh_3 (6.15 g, 23.47 mmol) in anhydrous THF (220 mL) under argon was added dropwise a solution of 2-bromo-1-*p*-tolylethanone (5 g, 23.47 mmol) in THF (60 mL). The reaction was refluxed for 2.5 h and then cooled to rt. The precipitate was collected by filtration and rinsed with diethyl ether. The solids were suspended in 1:1 MeOH and H_2O (500 mL), and then 2 N aq NaOH (55 mL) was added. The reaction was stirred at rt for 16 h. MeOH was removed *in vacuo* and the aq solution was extracted with $CHCl_3$. The combined organic extracts were washed with sat'd aq NaCl, dried over anhydrous Na_2SO_4, filtered and concentrated to provide Intermediate 2D (9 g, 97%) as a white solid. LCMS Anal. Calc'd for $C_{27}H_{23}OP$ 394.44, found [M+H] 395.2.

Intermediate 2E. (Z)-4,4,4-Trifluoro-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)but-2-en-1-one

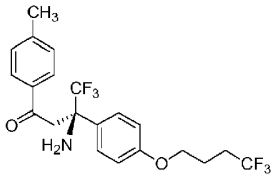
[0269]



[0270] Intermediate 2D (5.13 g, 13 mmol) and Intermediate 2C (3.90 g, 13 mmol) were suspended in DMSO (15 mL). The reaction was heated to 160 °C for 1000 s under microwave conditions. The reaction was cooled to rt and diluted with EtOAc (60 mL). The mixture was washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (120 g silica gel, elute with EtOAc in hexanes to provide Intermediate 2E (5.9 g, 98%) as a light brown oil.

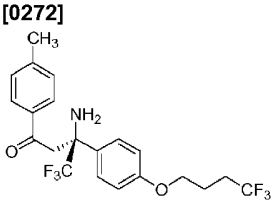
Intermediate 2F, isomer 1. (*R*)-3-Amino-4,4,4-trifluoro-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)-butan-1-one

[0271]



Intermediate 2F, isomer 2. ((*S*)-3-Amino-4,4,4-trifluoro-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)-butan-1-one

[0272]

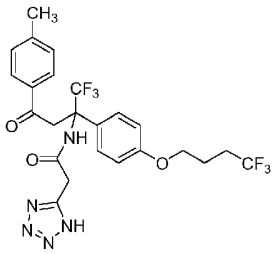


[0273] To a solution of Intermediate 2E (2.1 g, 5.04 mmol) in DMSO (50 mL) was added 15 N aq NH_4OH (25 mL). The mixture

was stirred in sealed pressure vessel for 2 days. The reaction was diluted with EtOAc (60 mL), washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography column (eluted with EtOAc in hexanes to provide racemic Intermediate 2F (2.2 g, 101%) as a white solid. LCMS Anal. Calc'd for $C_{21}H_{21}F_6NO_2$ 433.39, found [M+H] 434.2. Separation of the individual enantiomers of Intermediate 2F was carried out using preparative chiral SFC method A: Racemic Intermediate 2F (2200 mg) provided Intermediate 2F, isomer 1 (817 mg) and Intermediate 2F, isomer 2 (790 mg). Enantiomeric purity determination of Intermediate 2F, isomer 1 and 2 was carried out using analytical SFC method A. Intermediate 2F, isomer 1: RT = 2.2 min, 99% ee. Intermediate 2F, isomer 2: RT = 2.8 min, 99% ee. X-ray crystal data collected for the camphorsulfonic acid salt of Intermediate 2F, isomer 1 showed the chiral center to have the *R*-configuration; therefore, the chiral center for Intermediate 2F, isomer 2 has the *S*-configuration.

Intermediate 2G. 2-(1*H*-Tetrazol-5-yl)-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)-phenyl)butan-2-yl)acetamide

[0274]



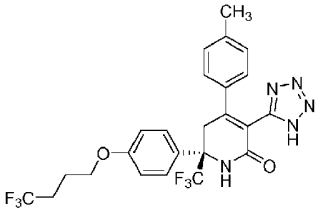
[0275] To a solution of Intermediate 2F (789 mg, 1.82 mmol) in anhydrous THF (9 ml) at 0 °C was added DCC (1.13 g, 5.46 mmol). 2-Tetrazole acetic acid (700 mg, 5.46 mmol) was added dropwise as a suspension in anhydrous THF (8 mL). The reaction was stirred at 0 °C for 1 h and then at rt overnight. The reaction was filtered and solids were rinsed with THF. The filtrate was diluted with EtOAc (40 mL), washed with sat'd Na_2CO_3 and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated to provide Intermediate 2G (1.5 g, 152%) as a reddish brown solid. Intermediate 2G was used in the next step without further purification. LCMS Anal. Calc'd for $C_{24}H_{23}F_6N_5O_3$ 543.46, found [M+H] 543.9.

Example 2

[0276] To a solution of Intermediate 2G (1.5 g) in EtOH (11 mL) was added piperidine (0.33 mL). The reaction was heated to 78 °C for 16 h in a sealed vial. The reaction was cooled to rt and the solvent was removed *in vacuo*. The residue was purified by preparative HPLC (MeOH/H_2O/TFA). Fractions containing the product were dried *in vacuo* and the product was re-dissolved in MeOH and concentrated again. The oily brown product was re-dissolved in CH_2Cl_2 (5 mL) and concentrated *in vacuo* to provide Example 2 (552 mg, 57% over 2 steps) as a reddish foam. LCMS Anal. Calc'd for $C_{24}H_{21}F_6N_5O_2$ 525.45, found [M+H] 526.2. ^{1}H NMR (500 MHz, CD_3OD) δ 7.61 (d, *J* = 9.1 Hz, 2H), 7.11 *(d, J*= 8.0 Hz, 2H), 7.07 - 7.01 (m, 2H), 6.90 *(d, J*= 8.3 Hz, 2H), 4.10 (t, *J* = 6.1 Hz, 2H), 3.84 - 3.64 (m, 2H), 2.48 - 2.35 (m, 2H), 2.30 (s, 3H), 2.14 - 2.00 (m, 2H).

Example 2-1. (*S*)-3-(1*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

[0277]

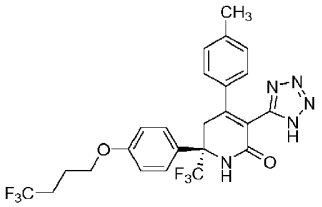


[0278] Separation of the individual enantiomers of Example 2 was carried out using preparative chiral SFC method C: Racemic Example 2 (89 mg) provided Example 2-1 (21 mg). Enantiomeric purity determination of Example 2-1 was carried out using analytical SFC method C. RT = 6.0 min, 99% ee.

[0279] Example 2-1 can be alternatively obtained from Intermediate 2F, isomer 2 using a sequence similar to one used for the conversion of Intermediate 2F to Example 2.

Example 2-2. (*R*)-3-(1*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

[0280]

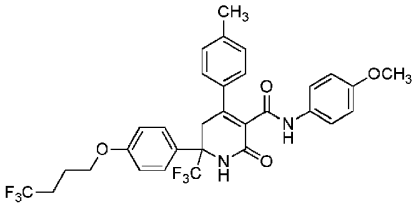


[0281] Separation of the individual enantiomers of Example 2 was carried out using preparative chiral SFC method C: Racemic Example 2 (89 mg) provided Example 2-2 (22 mg). Enantiomeric purity determination of Example 2-2 was carried out using analytical SFC method C. RT = 15.1 min, 99% ee.

[0282] Example 2-2 can be alternatively obtained from Intermediate 2F, isomer 1 using a sequence similar to one used for the conversion of Intermediate 2F to Example 2.

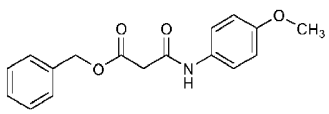
Example 6. *N*-(4-Methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoro-methyl)-1,2,5,6-tetrahydropyridine-3-carboxamide

[0283]



Intermediate 6A. Benzyl 3-(4-(methylamino)phenylamino)-3-oxopropanoate

[0284]

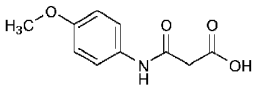


[0285] To a solution of monobenzyl malonate (12.2 g, 63.1 mmol) and DMF (90 µL) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added 2 M oxalyl chloride (35 mL, 70 mmol) in CH_2Cl_2. The reaction was stirred at 0 °C for 30 min, then at rt for 2.5 h. The solvent was removed *in vacuo* to provide freshly prepared acid chloride. This was dissolved in anhydrous CH_2Cl_2 (50 mL) and added dropwise to a solution of 4-methoxyaniline (7.76 g, 63 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C followed by the addition of pyridine (5.35 mL, 66.2 mmol). The reaction was stirred at 0 °C for 0.5 h, then at rt overnight. The reaction was washed with

water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was triturated with EtOAc/ CH_2Cl_2 to yield the first batch of Intermediate 6A as a light brown solid (6.95 g). The supernatant was evaporated and the residue was purified by silica gel chromatography (eluted with EtOAc in hexanes) to provide a second batch of Intermediate 6A as a light brown solid (7.4 g). The combined yield was 14.4 g (76%). LCMS Anal. Calc'd for $C_{17}H_{18}N_2O_3$ 298.34, found [M+H] 300.2.

Intermediate 6B. 3-(4-Methoxyphenylamino)-3-oxopropanoic acid

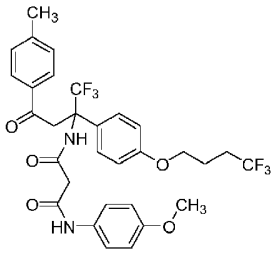
[0286]



[0287] To a solution of Intermediate 6A (14.4 g, 4.8 mmol) in 10:1 EtOAc/MeOH (220 mL) was added 10% Pd/C (250 mg). The reaction mixture was stirred vigorously under an atmosphere of hydrogen (40 psi) for 2 h. More 10% Pd/C (250 mg) was added and the reaction was stirred under 50 psi hydrogen for another 1 h. Additional 10% Pd/C (500 mg) was added and the reaction was stirred under 50 psi hydrogen for an additional 1 h. The reaction was filtered through a pad of Celite® and the filtrate was concentrated *in vacuo* to yield Intermediate 6B (11.1 g, 96%) as an off-white solid. LCMS Anal. Calc'd for $C_{10}H_{11}NO_4$ 209.20, found [M+H] 210.1.

Intermediate 6C. N^1-(4-Methoxyphenyl)-N^3-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluoro-butoxy)phenyl)-butan-2-yl)malonamide

[0288]



[0289] To triphenylphosphine (8.42 g, 32.1 mmol) in anhydrous CH_2Cl_2 (70 mL) was added Intermediate 6B (2.24 g, 10.7 mmol) in anhydrous CH_2Cl_2 (30 mL) followed by trichloroacetonitrile (1.86 g, 12.8 mmol). The mixture was stirred at rt for 3 h. The freshly prepared acid chloride was added to a solution of Intermediate 2F (1.13 g, 2.61 mmol) in anhydrous CH_2Cl_2 (20 mL), followed by the addition of pyridine (1.04 mL, 1.02 g, 12.85 mmol). The reaction was stirred at rt under argon overnight. The reaction was cooled to 0 °C and MeOH (40 mL) was added. The reaction was stirred at 0 °C for 10 min, then at rt for 30 min. The solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography (120 g silica gel, eluted with EtOAc in hexanes). Product and triphenylphosphine oxide co-eluted. Fractions containing both were combined and evaporated to dryness. The solids were triturated with hexanes/EtOAc to remove most of the triphenylphosphine oxide. The product was again purified by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 6C (1.03 g, 63%) as a brown oil. LCMS Anal. Calc'd for $C_{31}H_{30}F_6N_2O_5$ 624.57, found [M+H] 625.3.

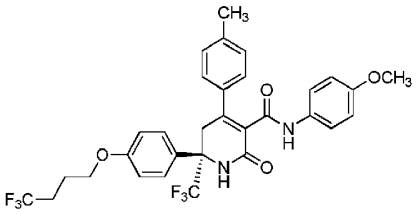
Example 6

[0290] To a solution of Intermediate 6C (1.03 g, 1.65 mmol) in MeOH (10 mL) was added piperidine (100 µL, 1.01 mmol). The reaction was stirred at 75 °C for 1 h. The solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography (120 g silica gel, eluted with EtOAc in hexanes). Mixed fractions from the first column were purified again by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to provide Example 6 (546 mg, 55%) as a off-white solid. LCMS Anal. Calc'd for $C_{31}H_{28}F_6N_2O_4$ 606.56, found [M+H] 607.3. ^{1}H NMR (500 MHz, CD_3OD) δ 1.97-2.08 (m, 2 H), 2.30 (s, 3 H),

2.32-2.44 (m, 2 H), 3.45-3.67 (m, 2 H), 3.72 (s, 3 H), 4.06 (t, *J* = 6.05 Hz, 2 H), 6.77 (d, *J* = 9.35 Hz, 2 H), 6.97 (d, *J* = 8.80 Hz, 2 H), 7.13-7.24 (m, 4 H), 7.28 (d, *J*= 8.25 Hz, 2 H), 7.52 (d, *J*= 8.80 Hz, 2 H).

Example 6-1. (*R*)-*N*-(4-Methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoro-methyl)-1,2,5,6-tetrahydropyridine-3-carboxamide

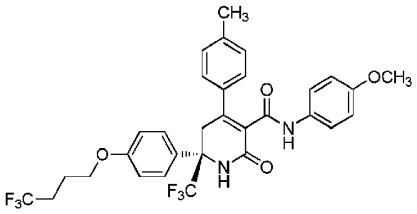
[0291]



[0292] Example 6-1 was prepared using a procedure analogous to Example 6 by replacing Intermediate 2F with Intermediate 2F, isomer 1.

Example 6-2. (*S*)-*N*-(4-Methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoro-methyl)-1,2,5,6-tetrahydropyridine-3-carboxamide

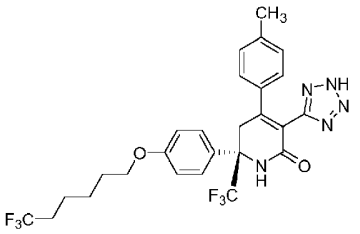
[0293]



[0294] Example 6-2 was prepared using a procedure analogous to Example 6 by replacing Intermediate 2F with Intermediate 2F, isomer 2.

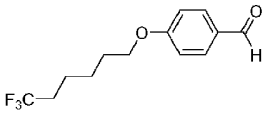
Example 8. (*S*)-3-(2*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(4-(6,6,6-trifluorohexyloxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

[0295]



Intermediate 8A. 4-(6,6,6-Trifluorohexyloxy)benzaldehyde

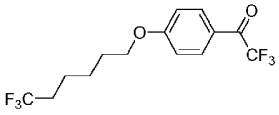
[0296]



[0297] To a suspension of 4-hydroxybenzaldehyde (488 mg, 4 mmol) and 6-bromo-1,1,1-trifluorohexane (657 mg, 3 mmol) in MeCN (10 mL) was added K_2CO_3 (829 mg, 6.00 mmol). The resulting mixture was reflux overnight. Insoluble material was filtered off and rinsed with MeCN. The combined filtrate was concentrated to afford a white solid. This white solid was partitioned between EtOAc and 1 N NaOH solution. The organic layer was separated, washed with sat'd NH_4Cl, dried over $MgSO_4$, filtered and concentrated to afford Intermediate 8A as a clear liquid. LCMS Anal. Calc'd for $C_{13}H_{15}F_3O_2$ 260.10, found [M+H] 261.0.

Intermediate 8B. 2,2,2-Trifluoro-1-(4-(6,6,6-trifluorohexyloxy)phenyl)ethanone

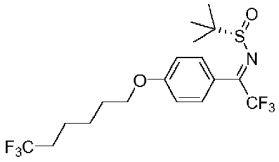
[0298]



[0299] Intermediate 8B was prepared using a procedure analogous to Intermediate 2C except that Intermediate 2A was replaced with Intermediate 8A. ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 - 8.02 (m, 2 H), 6.99 - 6.97 (m, 1 H), 4.08 (t, *J* = 6.2 Hz, 2 H), 2.19 - 2.06 (m, 2 H), 1.92 - 1.82 (m, 2 H), 1.71 - 1.55 (m, 4 H).

Intermediate 8C. (*S*,*E*)-2-Methyl-*N*-(2,2,2-trifluoro-1-(4-(6,6,6-trifluorohexyloxy)phenyl)ethylidene)propane-2-sulfinamide

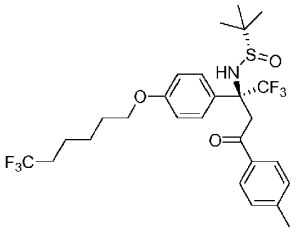
[0300]



[0301] To a solution of Intermediate 8B (717 mg, 2.184 mmol) and (*S*)-2-methylpropane-2-sulfinamide (529 mg, 4.37 mmol) in THF (10 mL) was added tetraethoxytitanium (1993 mg, 8.74 mmol) in THF (20 mL). The resulting mixture was reflux for 5 h. TLC (20% EtOAc in hexane) indicated the starting ketone was completely consumed. The solvent was evaporated to afford a yellow oil. This yellow oil was dissolved in EtOAc and then washed with saturated $NaHCO_3$ (25 mL) and a large amount of white precipitation formed which was removed by filtering through a bed of Celite®. The white precipitation was rinsed with EtOAc. The combined EtOAc solution was washed again with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to afford Intermediate 8C (620 mg, 66%).

Intermediate 8D. (*S*)-2-Methyl-*N*-((*S*)-1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(6,6,6-trifluorohexyloxy)phenyl)butan-2-yl)propane-2-sulfinamide

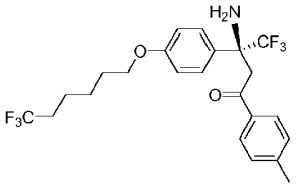
[0302]



[0303] To a solution of 1-(*p*-tolyl)ethanone (609 mg, 4.31 mmol) in THF (10 mL) was cooled to -78 °C and to this solution was added lithium bis(trimethylsilyl)amide (4.31 mL, 4.31 mmol). The resulting mixture was stirred at -78 °C for 20 min and then Intermediate 8C (620 mg, 1.437 mmol) in THF (3 mL) was added dropwise. The resulting mixture was stirred at -78 °C for 1.5 h and then at 0 °C for 1.5 h. The reaction was quenched with NH_4Cl and concentrated. The crude product was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes) to afford Intermediate 8D (482 mg, 59%) as the slower eluting diastereomer on silica gel column. LCMS Anal. Calc'd for $C_{27}H_{33}F_6NO_3S$ 565.21, found [M+H] 566.0.

Intermediate 8E. (*S*)-3-Amino-4,4,4-trifluoro-1-*p*-tolyl-3-(4-(6,6,6-trifluorohexyloxy)phenyl)butan-1-one

[0304]



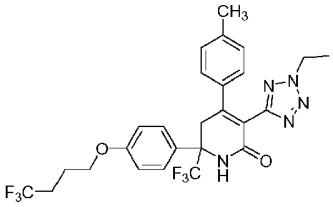
[0305] To a solution of Intermediate 8D (482 mg, 0.852 mmol) in MeOH (4 mL) was added 4 M HCl (1 mL, 4.00 mmol) in dioxane. The resulting mixture was stirred at rt for 2 h and then concentrated. The residue was taken up in EtOAc, washed with saturated $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated to afford Intermediate (386 mg, 58%) as a colorless oil, which was used for the subsequent reaction without further purification. LCMS Anal. Calc'd for $C_{23}H_{25}F_6NO_2$ 461.18, found [M+H] 461.9.

Example 8

[0306] To a solution of Intermediate 8E (140 mg, 0.303 mmol) and 2-(2*H*-tetrazol-5-yl)acetic acid (117 mg, 0.910 mmol) in THF (3 mL) at 0 °C was added DCC (188 mg, 0.910 mmol). The resulting mixture was stirred overnight. The solvent was evaporated and the crude mixture was taken up in EtOAc. The organic solution was washed with saturated $NaHCO_3$, 1 N HCl and brine, dried ($MgSO_4$), filtered and concentrated to afford a brown oil. This oil was dissolved in EtOH (3 mL) and added piperidine (300 µL, 3.03 mmol). The resulting mixture was stirred at 80 °C overnight. The reaction mixture was diluted with MeOH and purified by preparative HPLC (MeCN/H_2O/TFA) to yield Example 8 (86 mg, 51%) as a solid. LCMS Anal. Calc'd for $C_{26}H_{25}F_6N_5O_2$ 553.19, found [M+H] 554.0. ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.8 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 3 H), 7.02 - 6.93 (m, 4 H), 3.99 (t, *J* = 6.3 Hz, 2 H), 3.68 - 3.56 (m, 2 H), 2.39 (s, 3 H), 2.19 - 2.07 (m, 2 H), 1.89 - 1.79 (m, 2 H), 1.71 - 1.63 (m, 2 H), 1.62 - 1.53 (m, 2 H).

Example 9. 3-(2-Ethyl-2*H*-tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

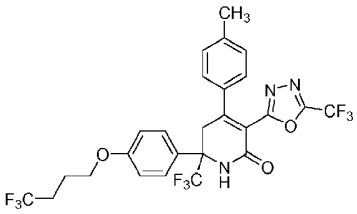
[0307]



[0308] To Example 2 (30 mg, 0.057 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was added iodoethane (9 mg, 0.057 mmol) and triethylamine (24 µL, 0.17 mmol). The reaction was heated to 120 °C for 10 min under microwave conditions. The solvent was evaporated *in vacuo* and the residue was purified by preparative HPLC (CH_3CN/H_2O/TFA) to provide Example 9 (2.3 mg, 7%) as a light brown solid. LCMS Anal. Calc'd for $C_{26}H_{25}F_6N_5O_2$ 553.50, found [M+H] 554.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (t, *J*= 7.42 Hz, 2 H), 1.98 - 2.13 (m, 2 H), 2.21 - 2.39 (m, 5 H), 3.51 (d, *J* = 17.60 Hz, 1 H), 3.72 (d, *J*= 17.60 Hz, 1 H), 4.04 (t, *J*= 6.05 Hz, 2 H), 4.56 (q, *J*= 7.52 Hz, 2 H) 6.87 (d, *J*= 8.25 Hz, 2 H), 6.95 (d, *J* = 8.80 Hz, 2 H), 7.02 (d, *J* = 8.25 Hz, 2 H), 7.46 (d, *J* = 8.80 Hz, 2 H), 7.93 (s, 1 H).

Example 10. 4-*p*-Tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-5,6-dihydropyridin-2(1*H*)-one

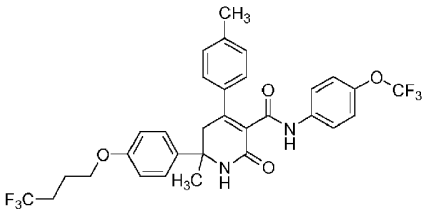
[0309]



[0310] To Example 2 (29 mg, 0.055 mmol) in anhydrous CH_2Cl_2 (0.3 mL) was added a solution of trifluoroacetic anhydride (23.2 mg, 0.11 mmol) in anhydrous CH_2Cl_2 (0.2 mL) dropwise. The mixture was stirred at rt for 4 h and then concentrated. The residue was purified by preparative HPLC to provide Example 10 (19 mg, 58%) as a white solid. LCMS Anal. Calc'd for $C_{26}H_{20}F_9N_3O_3$ 593.44, found [M+H] 594.2. ^{1}H NMR (500 MHz, CD_3OD) δ 1.97 - 2.11 (m, 2 H), 2.31 (s, 3 H), 2.34 - 2.44 (m, 2 H), 3.64 - 3.88 (m, 2 H), 4.08 (t, *J*= 6.05 Hz, 2 H), 6.98 (d, *J*= 8.25 Hz, 2 H), 7.03 (d, *J*= 8.80 Hz, 2 H), 7.16 (d, *J* = 8.25 Hz, 2 H), 7.57 (d, *J*= 8.80 Hz, 2 H).

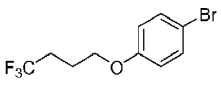
Example 11. 6-Methyl-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-*N*-(4-(trifluoromethoxy)-phenyl)-1,2,5,6-tetrahydropyridine-3-carboxamide

[0311]



Intermediate 11A. 1-Bromo-4-(4,4,4-trifluorobutoxy)benzene

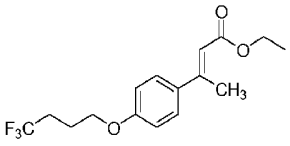
[0312]



[0313] To a solution of 4-bromophenol (2.2 g, 12.7 mmol) and 4-bromo-1,1,1-trifluorobutane (2.4 g, 12.7 mmol) in anhydrous DMF (15 mL) was added K_2CO_3 (3.5 g, 25.4 mmol). The mixture was stirred at rt overnight. The mixture was diluted with EtOAc (120 mL) and the solids were removed by filtration. The filtrate was washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (40 g silica gel, eluted with EtOAc in hexanes) to provide Intermediate 11A (3.05 g, 85%) as a colorless oil.

Intermediate 11B. (*E*)-Ethyl 3-(4-(4,4,4-trifluorobutoxy)phenyl)but-2-enoate

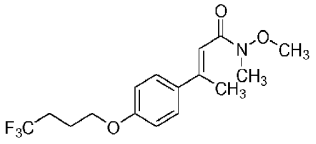
[0314]



[0315] Intermediate 11A (2.81 g, 9.93 mmol), (*E*)-ethyl but-2-enoate (1.25 g, 10.9 mmol), palladium(II) acetate (0.11 g, 0.5 mmol), tetraethylammonium chloride (1.65 g, 9.9 mmol), *N*-cyclohexyl-*N*-methylcyclohexanamine (2.91 g, 14.9 mmol) and dimethylacetamide (30 ml) were placed in a oven-dried vial and sparged with argon for 5 min. The vial was sealed and the reaction heated to 110 °C for 6 h. The reaction was cooled to rt, diluted with EtOAc (75 mL), washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc in hexanes to provide Intermediate 11B (1.81 g, 49%) as a colorless oil. LCMS Anal. Calc'd for $C_{16}H_{19}F_3O_3$ 316.32, found [M+H] 317.2.

Intermediate 11C. (*E*)-*N*-Methoxy-*N*-methyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)but-2-enamide

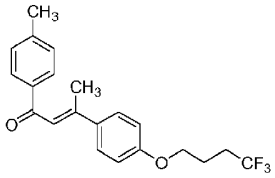
[0316]



[0317] A solution of Intermediate 11B (2.67 g, 8.44 mmol) and *N,O*-dimethylhydroxylamine hydrochloride (1.65 g, 16.9 mmol) in anhydrous THF (35 mL) was cooled to -61°C ($CHCl_3$/dry ice) under an atmosphere of Ar. To this solution was added 0.5 M isopropylmagnesium chloride (16.9 mL, 33.8 mmol) in THF slowly via a syringe. The reaction was stirred at -61 °C for 1.5 h, warmed to -20 °C (sat'd aq NaCl/ice) and stirred for 40 min, then warmed to 0 °C and stirred for 20 min. The reaction was poured into 10 mL of sat'd aq NH_4Cl and 12 mL of water, and then extracted with EtOAc. The organic layer was washed with sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc in hexanes to provide Intermediate 11C (1.62 g, 58%) as a light brown oil. LCMS Anal. Calc'd for $C_{16}H_{20}F_3NO_3$ 331.33, found [M+H] 332.2.

Intermediate 11D. (*E*)-1-*p*-Tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)but-2-en-1-one

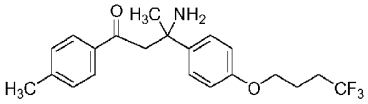
[0318]



[0319] To a solution of Intermediate11C (1.62 g, 4.89 mmol) in anhydrous THF (25 mL) at -78 °C was added dropwise 0.5 M *p*-tolylmagnesium bromide in ether (25 mL, 12.5 mmol). The reaction was stirred at -78 °C for 40 min, then gradually warmed to rt. The reaction was poured into 1:1 sat'd aq NH_4Cl and water (60 mL). The mixture was extracted with EtOAc. The organic layer was washed with sat'd aq NaCl, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (eluted with EtOAc in hexanes) to provide Intermediate 11D (1.34 g, 76%) as a light brown solid. LCMS Anal. Calc'd for $C_{21}H_{21}F_3O_2$ 362.39, found [M+H] 363.2. ^1H NMR (500 MHz, $CDCl_3$) δ 2.01 - 2.11 (m, 2 H), 2.29 - 2.37 (m, 2 H), 2.42 (s, 3 H), 2.58 (s, 3 H), 4.07 (t, *J*= 6.05 Hz, 2 H), 6.92 (d, *J*= 8.80 Hz, 2 H), 7.14 (s, 1 H), 7.23 - 7.34 (m, *J*= 8.25 Hz, 2 H), 7.55 (d, *J*= 8.80 Hz, 2 H), 7.90 (d, *J*= 8.25 Hz, 2 H).

Intermediate 11E. 3-Amino-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)butan-1-one

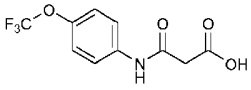
[0320]



[0321] Ammonia was bubble into a solution of Intermediate 11D (1.34 mg, 0.64 mmol) in EtOH (20 mL) and DMSO (12 mL) for 10 min at 0 °C. The reaction was stirred at rt overnight in a sealed pressure vessel. Analytical HPLC showed reaction to have progressed only ca. 10%. The mixture was cooled to -15 °C, then ammonia was bubbled through for 7 min. The vessel was sealed and the reaction was stirred at rt overnight. Analytical HPLC showed the reaction to be ca. 25-30% complete. The mixture was diluted with EtOAc (75 mL), washed with water and sat'd aq NaCl, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to provide Intermediate11E (281 mg, 20%) as a light brown oil. LCMS Anal. Calc'd for $C_{21}H_{24}F_3NO_2$ 379.42, found [M+H] 380.3.

Intermediate 11F. 3-Oxo-3-(4-(trifluoromethoxy)phenylamino)propanoic acid

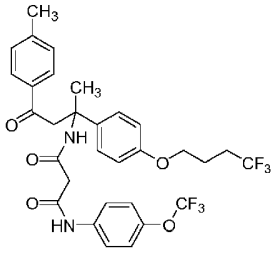
[0322]



[0323] By sequential application of the procedures for Intermediates 6A and 6B, 4-trifluoromethoxyaniline (2.3 g, 13 mmol) was converted to Intermediate 11F (2.8 g, 11 mmol), which was isolated as a white solid. LCMS Anal. Calc'd for $C_{10}H_8F_3NO_4$ 263.17, found [M+H] 264.1.

Intermediate 11 G. N^1-(4-Oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)-N^3-(4-(trifluoromethoxy)-phenyl)malonamide

[0324]



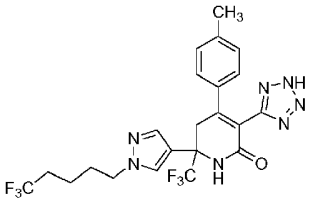
[0325] To a solution of Intermediate 11F (41.6 mg, 0.158 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was added PPh_3 (124 mg, 0.474 mmol) followed by dropwise addition of trichloroacetonitrile (27.4 mg, 0.19 mmol). The reaction was stirred at rt for 3 h. To the freshly prepared acid chloride was added a solution of Intermediate 11E (20 mg, 0.053 mmol) in anhydrous CH_2Cl_2 (0.3 mL) followed by pyridine (19 µL, 0.237 mmol). The mixture was stirred at rt overnight. The solvent was removed *in vacuo*. The product was purified by preparative HPLC (MeOH/H_2O/TFA) to yield Intermediate 11 G (11 mg, 33%) as a brown solid. LCMS Anal. Calc'd for $C_{31}H_{30}F_6N_2O_5$ 624.57, found [M+H] 625.4.

Example 11

[0326] To a solution of Intermediate 11G (11 mg, 0.018 mmol) in MeOH (0.8 ml) was added piperidine (15 µL). The reaction was stirred at 75 °C for 1.5 h. The product was isolated by preparative HPLC (CH_3CN/H_2O/TFA) to provide Example 11 (5.2 mg, 44%) as a brown solid. LCMS Anal. Calc'd for $C_{31}H_{28}F_6N_2O_4$ 606.56, found [M+H] 607.4. ^{1}H NMR (500 MHz, CD_3OD) δ 1.68 (s, 3 H), 1.95 - 2.07 (m, 2 H), 2.27 (s, 3 H), 2.30 - 2.41 (m, 2 H), 3.11 - 3.26 (m, 2 H), 4.03 (t, *J*= 6.05 Hz, 2 H), 6.91 (d, *J*= 8.80 Hz, 2 H), 7.08 - 7.18 (m, 4 H), 7.22 (d, *J* = 8.25 Hz, 2 H), 7.38 (d, *J* = 8.80 Hz, 2 H), 7.45 (d, *J* = 8.80 Hz, 2 H).

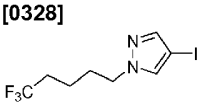
Example 12. 3-(2*H*-Tetrazol-5-yl)-4-*p*-tolyl-6-(trifluoromethyl)-6-(1-(5,5,5-trifluoropentyl)-1*H*-pyrazol-4-yl)-5,6-dihydropyridin-2(1*H*)-one

[0327]



Intermediate 12A. 4-Iodo-1-(5,5,5-trifluoropentyl)-1*H*-pyrazole

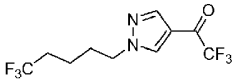
[0328]



[0329] To a stirred solution of 4-iodo-1*H*-pyrazole (337 mg, 1.737 mmol) in DMF (10 mL) was added sodium hydride (104 mg, 2.61 mmol). After 30 min, 5-bromo-1,1,1-trifluoropentane (427 mg, 2.085 mmol) was added. The reaction was stirred at rt for 2 h. 3:1 hexane:ether and water were added. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by silica gel chromatography (24 g silica gel, eluted with 0-60% EtOAc in hexanes) to give the desired product (460 mg, 83%) as clear oil. LCMS Anal. Calc'd for $C_8H_{10}F_3IN_2$ 318.0, found [M+H] 319.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1 H), 7.40 (s, 1 H), 4.12 (t, *J* = 6.9 Hz, 2 H), 2.00 - 2.15 (m, 2 H), 1.85 - 1.96 (m, 2 H), 1.47 - 1.61 (m, 2 H).

Intermediate 12B. 2,2,2-Trifluoro-1-(1-(5,5,5-trifluoropentyl)-1*H*-pyrazol-4-yl)ethanone

[0330]



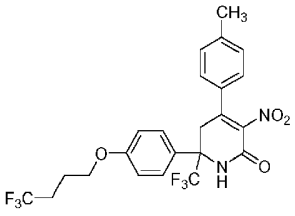
[0331] To a stirred solution of Intermediate 12A (460 mg, 1.446 mmol) in tetrahydrofuran (5 mL) at 0 °C was added isopropylmagnesium chloride (0.795 mL, 1.591 mmol) quickly. After 30 min, additional 0.25 eq of *i*PrMgCl was added and after 30min, the mixure was cooled to -78 °C. 2,2,2-Trifluoro-1-(piperidin-1-yl)ethanone (288 mg, 1.591 mmol) was added quickly and the reaction was warmed to rt and stirred for 3 h. The reaction was quenched with sat'd aq NH_4Cl and diluted with EtOAc. The organic layer was washed with sat'd aq NH_4Cl, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by silica gel chromatography (40 g silica gel, eluted with 0-100% EtOAc in hexanes) to give the desired product (265 mg, 64%) as clear oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (s, 2 H), 4.22 (t, *J* = 7.0 Hz, 2 H), 2.07 - 2.20 (m, 2 H), 1.98 - 2.05 (m, 2 H), 1.55 - 1.65 (m, 2 H).

Example 12

[0332] Example 12 was prepared using a procedure analogous to Example 2 by replacing Intermediate 2C with Intermediate 12B. LCMS Anal. Calc'd for $C_{22}H_{21}F_6N_7O$ 513.2, found [M+H] 514.3. ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.63 (s, 1 H), 7.54 - 7.59 (m, 1 H), 7.06 (d, *J* = 8.0 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 4.16 (t, *J* = 7.0 Hz, 2 H), 3.58 (d, *J* = 18.2 Hz, 1 H), 3.39 (d, *J* = 17.9 Hz, 1 H), 2.28 (s, 3 H), 2.02 - 2.17 (m, 2 H), 1.93 (quin, *J* = 7.4 Hz, 2 H), 1.46 - 1.55 (m, 2 H).

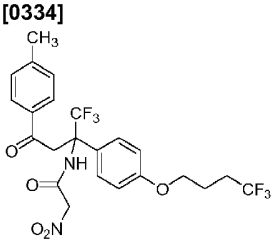
Example 13. 3-Nitro-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

[0333]



Intermediate 13A. 2-Nitro-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)-acetamide

[0334]



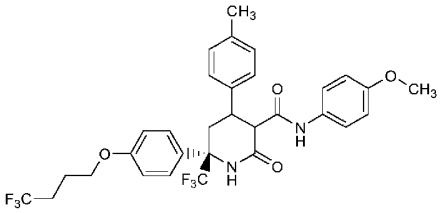
[0335] To a solution of Intermediate 2F (130 mg, 0.3 mmol) in anhydrous THF (1 mL) at 0 °C was added DCC (204 mg, 0.99 mmol) followed by a solution of 2-nitroacetic acid (104 mg, 0.99 mmol) in anhydrous THF (0.5 mL) dropwise. The reaction was stirred at 0 °C for 1 h then at rt overnight. The reaction was heated to 70 °C for 4 h. The reaction was cooled to rt and diluted with EtOAc (3 mL). The solids were filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluted with EtOAc in hexanes) to provide Intermediate 13A (129 mg, 83%) as a brown oil. LCMS Anal. Calc'd for $C_{23}H_{22}F_6N_2O_5$ 520.42, found [M+H] 521.1.

Example 13

[0336] To a solution of Intermediate 13A (126 mg, 0.24 mmol) in MeOH (2 mL) was added piperidine (35 µL). The reaction mixture was heated at 75 °C for 1.5 h. The product was isolated by preparative HPLC (MeOH/H_2O/TFA) to provide Example 13 (21 mg, 17%) as a off-white solid. LCMS Anal. Calc'd for $C_{23}H_{20}F_3N_2O_4$ 502.41, found [M+H] 503.1. ^{1}H NMR (500 MHz, CD_3OD) δ 1.98 - 2.08 (m, 2 H), 2.28 - 2.45 (m, 5 H), 3.58 (d, *J*= 17.60 Hz, 1 H), 3.76 (d, *J*= 17.60 Hz, 1 H), 4.08 (t, *J* = 6.05 Hz, 2 H), 7.02 (d, *J*= 8.80 Hz, 2 H), 7.12 - 7.19 (m, 2 H), 7.22 - 7.30 (m, 2 H), 7.53 (d, *J*= 8.80 Hz, 2 H).

Example 16-1 and Example 16-2. *N*-(4-Methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)piperidine-3-carboxamide

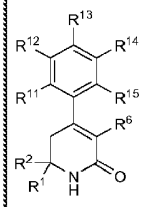
[0337]



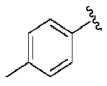
[0338] To a solution of Example 6-2 (90 mg, 0.15 mol) in MeOH (2 mL) was added 10% palladium on carbon (5 mg). The mixture was stirred under hydrogen (50 psi) overnight. Additional palladium on carbon (5 mg) was added and the reaction was stirred under hydrogen (50 psi) for an additional 1 h. The catalyst was removed by filtration through a pad of Celite® and the solution was concentrated *in vacuo*. The products were partly separated by preparative HPLC (CH_3CN/H_2O/TFA). Fractions containing the two products were combined and separated by chiral HPLC method D to provide Example 16-1 and Example 16-2. Data for Example 16-1: LCMS Anal. Calc'd for $C_{31}H_{30}F_6N_2O_4$ 608.57, found [M+H] 609.2. ^{1}H NMR (400 MHz, CD_3OD) δ 1.97 - 2.14 (m, 2 H), 2.25 (s, 3 H), 2.32 - 2.46 (m, 2 H), 2.54 - 2.69 (m, 2 H), 3.17 (td, *J* = 11.82, 3.85 Hz, 1 H), 3.60 (d, *J* = 11.54 Hz, 1 H), 3.71 (s, 3 H), 4.10 (t, *J* = 6.05 Hz, 2 H), 6.76 (d, *J*= 8.79 Hz, 2 H), 6.99 - 7.12 (m, 6 H), 7.13 - 7.23 (m, 2 H), 7.55 (d, *J* = 8.79 Hz, 2 H). Analytical chiral HPLC method D RT = 6.75 min, 99% ee. Data for Example 16-2: LCMS Anal. Calc'd for $C_{31}H_{30}F_6N_2O_4$ 608.57, found [M+H] 609.2. ^{1}H NMR (400 MHz, CD_3OD) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.20 (m, 2H), 7.19 - 7.15 (m, 2H), 7.14 - 7.10 (m, 2H), 7.02 - 6.97 (m, 2H), 6.81 - 6.75 (m, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.94 - 3.84 (m, 1H), 3.73 (s, 3H), 3.60 (d, *J* = 12.1 Hz, 1H), 2.90 (dd, *J*= 14.8, 3.3 Hz, 1H), 2.45 - 2.32 (m, 2H), 2.31 (dd, 1H, overlaps with peak at δ□ 2.27), 2.27 (s, 3H), 2.08 - 1.98 (m, 2H). Preparative chiral HPLC method D: RT = 10.9 min, 99% ee.

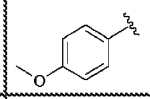
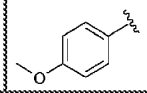
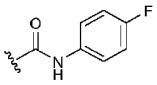
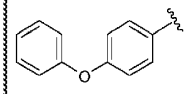
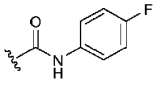
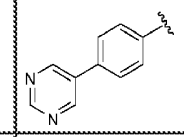
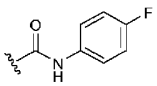
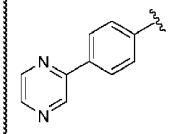
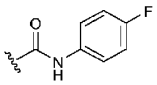
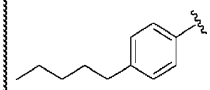
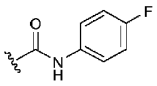
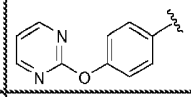
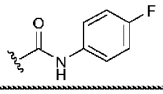
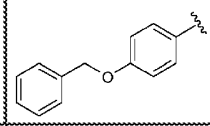
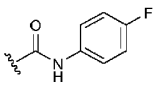
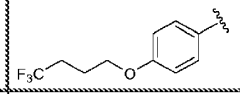
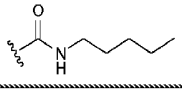
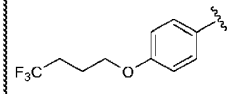
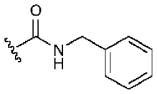
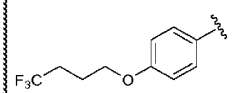
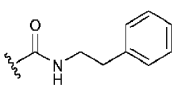
[0339] Examples 17-101 expressed by Formula (IIa), unless noted in the table, may be made by one skilled in the art by appropriate application of the procedures described for Examples 1-16. R^{11} to R^{15} are hydrogen, unless noted in the table.

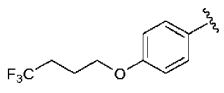
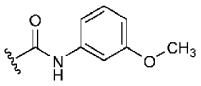
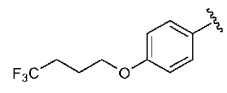
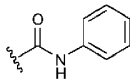
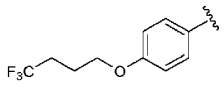
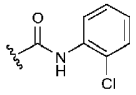
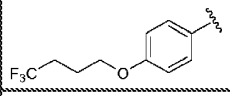
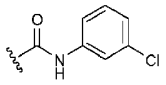
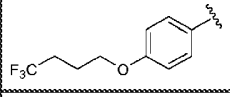
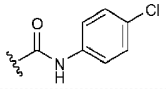
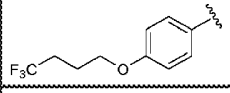
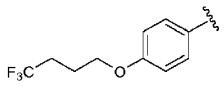
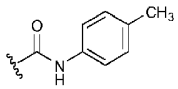
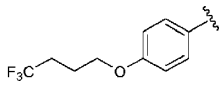
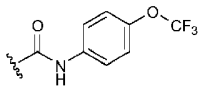
Table 2

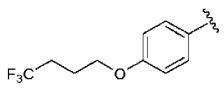
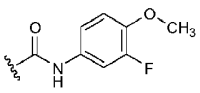
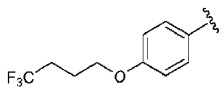
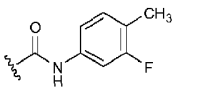
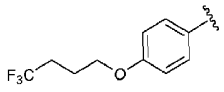
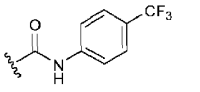
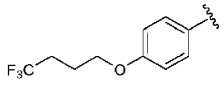
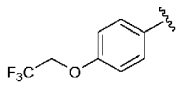
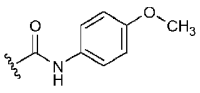
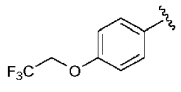
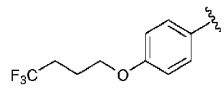
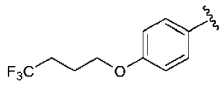


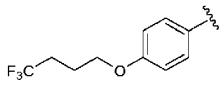
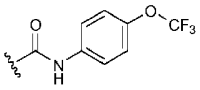
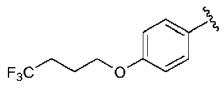
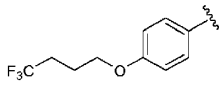
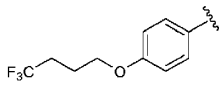
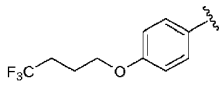
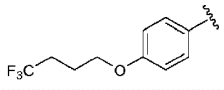
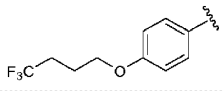
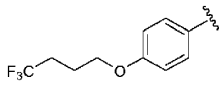
(IIa)

Example	R1	R2	R6	R11-R15	[M+H]	1HNMR (400 MHz, MeOD)
21 Rac		CH_3		$R^{13} = CH_3$	360.2	

Example	R1	R2	R6	R11-R15	[M+H]	1HNMR (400 MHz, MeOD)
38 Rac		CF_3		$R^{13} = CH_3$	430.1	
41 Rac		CF_3		$R^{13} = CH_3$	499.2	
48 Rac		CF_3		$R^{13} = CH_3$	561.4	2.36 (s, 3 H) 3.40 - 3.59 (m, 2 H) 6.82 (s, 1H) 6.93 (t, *J* = 8.79 Hz, 2 H) 7.01 - 7.13 (m, 5 H) 7.15-7.20 (m, 3 H) 7.34 - 7.45 (m, 4 H) 7.48 *(d, J* = 8.79 Hz, 2 H) 9.86 (s, 1 H).
49 Rac		CF_3		$R^{13} = CH_3$	547.4	2.30 (s, 3 H) 3.57-3.81 (m, 2 H) 6.96 (t, *J* = 8.79 Hz, 2 H) 7.17 (d, *J* = 7.70 Hz, 2 H) 7.27 - 7.38 (m, 4 H) 7.83 (m, 4H) 9.11 (s, 2H) 9.16 (s, 1 H).
50 Rac		CF_3		$R^{13} = CH_3$	547.4	
51 Rac		CF_3		$R^{13} = CH_3$	539.5	0.90 (t, *J* = 6.87 Hz, 3 H) 1.28-1.40 (m, 4 H) 1.58 - 1.71 (m, 2 H) 2.35 (s, 3 H) 2.55-2.71 (m, 2 H) 3.30-3.60 (m, 2 H) 6.63 (s, 1 H) 6.92 (t, *J* = 8.52 Hz, 2 H) 7.05 - 7.12 (m, 2 H) 7.14 - 7.20(m,2H)7.22-7.31(m, 2 H) 7.37 - 7.49 (m, 4 H) 9.94 (s, 1 H).
52 Rac		CF_3		$R^{13} = CH_3$	563.4	
54 Rac		CF_3		$R^{13} = CH_3$	575.3	
55 Rac		CF_3		$R^{13} = CH_3$	571.4	
56 Rac		CF_3		$R^{13} = CH_3$	591.3	
57 Rac		CF_3		$R^{13} = CH_3$	605.4	2.02 (dd, *J* = 9.90, 6.05 Hz, 2 H) 2.28 - 2.40 (m, 5 H) 2.45 -2.58 (m, 2 H) 3.12-3.35 (m, 2 H) 3.37 - 3.60 (m, 2 H) 4.05 (t, *J* = 6.05 Hz, 2 H) 6.91 - 7.01 (m, 4 H) 7.09 - 7.20 (m, 5 H) 7.21 - 7.26 (m, 2 H) 7.50 (d, *J* = 8.80 Hz, 2 H).

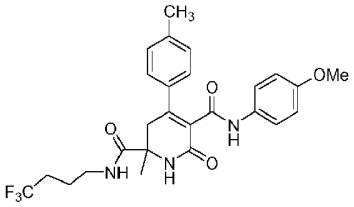
Example	R1	R2	R6	R11-R15	[M+H]	1HNMR (400 MHz, MeOD)
58 Rac		CF_3		$R^{13} = CH_3$	607.3	1.96 - 2.07 (m, 2 H) 2.26 - 2.32 (m, 3 H) 2.32 - 2.42 (m, 2 H) 3.45-3.67 (m, 2 H) 4.06 (t, *J* = 6.05 Hz, 2 H) 6.61 (dd, *J* = 8.25, 2.20 Hz, 1 H) 6.83 *(d, J* = 8.25 Hz, 1 H) 6.98 *(d, J* = 8.80 Hz, 2 H) 7.03 (s, 1 H) 7.09 (t, *J* = 8.25 Hz, 1 H) 7.16 (d, *J* = 8.25 Hz, 2 H) 7.28 *(d, J* = 8.25 Hz, 2 H) 7.52 (d, *J* = 8.80 Hz, 2 H).
59 Rac		CF_3		$R^{13} = CH_3$	577.3	1.95 - 2.08 (m, 2 H) 2.28 (s, 3 H) 2.32-2.42 (m, 2 H) 3.42 - 3.70 (m, 2 H) 4.05 (t, *J* = 6.05 Hz, 2 H) 6.97 *(d, J* = 8.80 Hz, 2 H) 7.00 - 7.06 (m, 1 H) 7.15 (d, *J* = 8.25 Hz, 2 H) 7.20 (t, *J* = 7.97 Hz, 2 H) 7.30 (dd, *J* = 16.77, 7.97 Hz, *4H)7.52(d,J=8.80Hz,2* H).
60 Rac		CF_3		$R^{13} = CH_3$	611.3	
61 Rac		CF_3		$R^{13} = CH_3$	611.3	
62 Rac		CF_3		$R^{13} = CH_3$	611.3	
70 Rac		CF_3	H	$R^{13} = CH_3$	458.2	
82 Rac		CF_3		$R^{13} = CH_3$	591.2	7.52 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.15 (d, *J* = 7.7 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 7.02 *(d, J* = 8.2 Hz, 2H), 6.98 (d, *J* = 7.7 Hz, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.64 *(d, J* = 17.0 Hz, 1H), 3.48 *(d, J*= 17.0 Hz, 1H), 2.39 - 2.32 (m, 2H), 2.29 (s, 3H), 2.24 (s, 3H), 2.06 - 1.98 (m, 2H).
83 Rac		CF_3		$R^{13} = CH_3$	661.2	7.53 *(d, J* = 8.8 Hz, 2H), 7.46 - 7.41 (m, 2H), 7.31 - 7.24 (m, *J* = 8.2 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.17 *(d, J* = 7.7 Hz, 2H), 7.01 - 6.96 (m, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.65 *(d, J* = 17.0 Hz, 1H), 3.50 *(d, J*= 17.0 Hz, 1H), 2.43 - 2.33 (m, 2H), 2.30 (s, 3H), 2.07 - 1.99 (m, 2H).

Example	R1	R2	R6	R11-R15	[M+H]	1HNMR (400 MHz, MeOD)
84 Rac		CF_3		$R^{13} = CH_3$	625.2	7.52 *(d, J* = 8.8 Hz, 2H), 7.30 - 7.24 (m, 3H), 7.17 *(d, J* = 7.7 Hz, 2H), 7.01 - 6.90 (m, 4H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.82 - 3.77 (s, 3H), 3.64 (d, *J* = 17.0 Hz, 1H), 3.49 (d, *J* = 17.0 Hz, 1H), 2.42 - 2.33 (m, 2H), 2.30 (s, 3H), 2.08 - 1.96 (m, 2H).
85 Rac		CF_3		$R^{13} = CH_3$	609.2	7.56 - 7.50 (ab quartet, *J* = 9.3 Hz, 2H), 7.30 - 7.20 (m, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.05 (t, *J* = 8.2 Hz, 1H), 7.01 - 6.95 (m, *J* = 8.8 Hz, 2H), 6.91 (dd, *J* = 8.2, 1.6 Hz, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.64 *(d, J* = 17.6 Hz, 1 H), 3.49 *(d, J* = 17.0 Hz, 1 H), 2.43 - 2.32 (m, 2H), 2.30 (s, 3H), 2.16 (s, 3H), 2.08 - 1.97 (m, 2H).
86 Rac		CF_3		$R^{13} = CH_3$	645.2	7.58 - 7.48 (m, 6H), 7.27 *(d, J* = 8.2 Hz, 2H), 7.15 *(d, J* = 8.2 Hz, 2H), 7.00 - 6.95 (m, 2H), 4.06 (t, *J* = 6.0 Hz, 2H), 3.65 *(d, J* = 17.6 Hz, 1H), 3.50 *(d, J*= 17.0 Hz, 1H), 2.43 - 2.31 (m, 2H), 2.28 (s, 3H), 2.09 - 1.95 (m, 2H).
87 Rac S-isomer		CF_3		$R^{13} = CH_3$	538.2	
88 Rac		CF_3		$R^{13} = CH_3$	579.2	2.31 (s, 3 H) 3.45-3.69 (m, 2 H) 3.70 - 3.76 (s, 3 H) 4.56 (q, J = 8.25 Hz, 2 H) 6.78 (d, J = 9.35 Hz, 2 H) 7.07 (d, J = 9.35 Hz, 2 H) 7.13-7.22 (m, 4 H) 7.29 (d, J = 8.25 Hz, 2 H) 7.59 (d, J = 8.80 Hz, 2 H).
90 Rac		CF_3		$R^{13} = CH_3$	498.1	2.28 (s, 3 H) 3.63 - 3.82 (m, 2 H) 4.58 (q, J = 8.61 Hz, 2 H) 6.88 (d, J = 8.25 Hz, 2 H) 7.10 (dd, J = 12.65, 8.80 Hz, 4 H) 7.65 (d, J = 8.80 Hz, 2 H).
92 Rac		CF_3		$R^{13} = OCH_2CH_3$	556.3	1.34 (t, J = 6.87 Hz, 3 H) 1.96 - 2.09 (m, 2 H) 2.26 - 2.43 (m, 2 H) 3.70 (s, 2 H) 3.98 (q, J = 6.78 Hz, 2 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.78 (d, J = 8.80 Hz, 2 H) 6.92 (d, J = 8.80 Hz, 2 H) 7.01 (d, J = 8.80 Hz, 2 H) 7.58 (d, J = 8.80 Hz, 2 H).
93 Rac		CF_3		$R^{13} = OCHF_2$	578.3	1.96-2.12 (m, 2 H) 2.28-2.45 (m, 2 H) 3.63 - 3.85 (m, 2 H) 4.07 (t, J = 6.05 Hz, 2 H) 6.95 - 7.08 (m, 7 H) 7.59 (d, J = 8.80 Hz, 2 H).

Example	R1	R2	R6	R11-R15	[M+H]	1HNMR (400 MHz, MeOD)
94 S-isomer		CF_3		$R^{13} = CH_3$	661.3	1.97 - 2.08 (m, 2 H) 2.29 (s, 3 H) 2.32 - 2.40 (m, 2 H) 3.50 (d, J = 17.05 Hz, 1 H) 3.65 (d, J = 17.60 Hz, 1 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.98 (d, J = 8.80 Hz, 2 H) 7.14 (dd, J = 16.77, 8.52 Hz, 4 H) 7.28 (d, J = 8.25 Hz, 2 H) 7.43 (d, J = 9.35 Hz, 2 H) 7.52 (d, J = 8.80 Hz, 2 H).
95 S-isomer		CF_3		$R^{11} = F$ $R^{13} =$ OCH_3	560.3	1.95 - 2.08 (m, 2 H) 2.28 - 2.42 (m, 2 H) 3.58 - 3.71 (m, 2 H) 3.76 (s, 3 H) 4.06 (t, J = 6.05 Hz, 2 H) 6.59 (dd, J = 12.92, 2.47 Hz, 1 H) 6.69 (dd, J = 8.80, 2.75 Hz, 1 H) 6.91 - 6.96 (m, 1 H) 7.00 (d, J = 8.80 Hz, 2 H) 7.57 (d, J = 8.80 Hz, 2 H).
96 Rac		CF_3		$R^{12} = CH_3$	526.3	
97 Rac		CF_3		All H	512.2	
98 Rac		CF_3		$R^{13} = CF_3$	580.3	7.60 (t, *J* = 8.2 Hz, 4H), 7.18 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.80 *(d, J* = 18.1 Hz, 1H), 3.69 (d, *J* = 18.1 Hz, 1H), 2.45 - 2.31 (m, 2H), 2.11 - 1.93 (m, 2H).
99 Rac		CF_3		$R^{12} = Cl$	546.2	
100 Rac		CF_3		$R^{12} =$ OCH_3	542.3	
101 Rac		CF_3		$R^{13} = Cl$	546.2	
*Data reported as molecular weight of compound based on electrospray mass spec results						

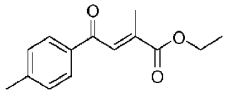
Example 102. N^5-(4-Methoxyphenyl)-2-methyl-6-oxo-4-*p*-tolyl-N^2-(4,4,4-trifluorobutyl)-1,2,3,6-tetrahydropyridine-2,5-dicarboxamide

[0340]



Intermediate 102A. (*E*)-Ethyl 2-methyl-4-oxo-4-*p*-tolylbut-2-enoate

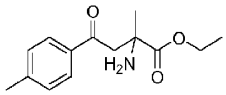
[0341]



[0342] A solution of Intermediate 2D (3.02 g, 7.65 mmol) and ethyl 2-oxopropanoate (0.74 g, 6.37 mmol) in THF (12 mL) in a 5 mL microwave vial equipped with a magnetic stirrer was heated at 150 °C under microwave conditions for 20 min. The solvent was removed under vacuum and the residue was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes) to provide the desired product (1.067 g, 72%) as a yellow oil. LCMS Anal. Calc'd for $C_{14}H_{16}O_3$ 232.11, found [M+H] 233.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.87 (d, *J* = 8.25 Hz, 2 H), 7.69 (q, *J* = 1.56 Hz, 1 H), 7.28 (d, *J* = 7.98 Hz, 2 H), 4.30 (q, *J* = 7.15 Hz, 2 H), 2.42 (s, 3 H), 2.16 *(d, J* = 1.38 Hz, 3 H), 1.36 (t, *J* = 7.02 Hz, 3 H).

Intermediate 102B. Ethyl 2-amino-2-methyl-4-oxo-4-*p*-tolylbutanoate

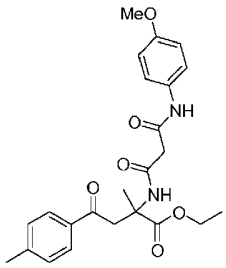
[0343]



[0344] To a solution of Intermediate 102A (1.067 g, 4.59 mmol) in DMSO (20 mL) under argon was added NH_4OH (18.04 mL, 271 mmol) and the reaction mixture was stirred at rt overnight. The reaction mixture was diluted with EtOAc (75 mL) and washed sequentially with water (40 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give a yellow oil. The oil was purified by silica gel chromatography (120 g silica gel) to provide the desired product (0.632 g, 55%) as a clear oil. LCMS Anal. Calc'd for $C_{14}H_{19}NO_3$ 249.14, found [M+H] 250.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.25 Hz, 2 H), 7.24 (d, *J* = 7.98 Hz, 2 H), 4.14 (dd, *J* = 7.15, 2.75 Hz, 2 H), 3.65 (d, *J* = 17.61 Hz, 1 H), 3.20 (d, *J* = 17.61 Hz, 1 H), 2.40 (s, 3 H), 2.18 - 2.27 (m, 2 H), 1.39 (s, 3 H), 1.19 (t, *J* = 7.01 Hz, 3 H).

Intermediate 102C. Ethyl 2-(3-(4-methoxyphenylamino)-3-oxopropanamido)-2-methyl-4-oxo-4-*p*-tolylbutanoate

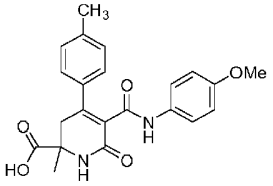
[0345]



[0346] To a solution of Intermediate 6B (0.388 g, 1.855 mmol) in DCM (10 mL) under argon was added 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-amine (0.293 g, 2.192 mmol) and the reaction mixtrue was stirred at rt for 20 min. A solution of Intermediate 102B (0.4204 g, 1.686 mmol) in DCM (1.000 mL) followed by pyridine (0.409 mL, 5.06 mmol) were added and the reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated to give a dark oil which was dissolved in EtOAc (15 mL) and washed with water (5 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel chromatography (80 g silica gel) to provide the desired product (0.650 g, 88%) as an orange oil. LCMS Anal. Calc'd for $C_{24}H_{28}N_2O_6$ 440.19, found [M+H] 441.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.25 Hz, 2 H), 7.24 (d, *J* = 7.98 Hz, 2 H), 4.14 (dd, *J* = 7.15, 2.75 Hz, 2 H), 3.65 (d, *J* = 17.61 Hz, 1 H), 3.20 *(d, J* = 17.61 Hz, 1 H), 2.40 (s, 3 H), 2.18 - 2.27 (m, 2 H), 1.39 (s, 3 H), 1.19 (t, *J* = 7.01 Hz, 3 H).

Intermediate 102D. 5-(4-Methoxyphenylcarbamoyl)-2-methyl-6-oxo-4-*p*-tolyl-1,2,3,6-tetrahydropyridine-2-carboxylic acid

[0347]



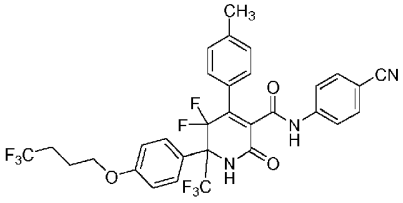
[0348] To a solution of Intermediate 102C (0.033 g, 0.075 mmol) in THF (8 mL) and water (1.600 mL) was added lithium hydroxide monohydrate (3.77 mg, 0.090 mmol) and the reaction mixture was stirred at rt for 1 h. The reaction mixture was acidified with AcOH (5 drops) and diluted with EtOAc (10 mL) and water (3 mL). The phases were separated and the aqueous phase was extracted with EtOAc (10 mL). The organic phases were combined and dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the desired product (0.0213 g, 72%) as a white solid. LCMS Anal. Calc'd for $C_{22}H_{22}N_2O_5$ 394.15, found [M+H] 395.0.

Example 102

[0349] To a solution of Intermediate 102D (0.0213 g, 0.054 mmol) in DCM (2 mL) under argon was added EDC (0.014 g, 0.076 mmol), HOBT (9.92 mg, 0.065 mmol), 4,4,4-trifluorobutan-1-amine (8.24 mg, 0.065 mmol), and DIEA (0.019 mL, 0.108 mmol). The reaction mixture was stirred at rt for 3 days. The reaction mixture was diluted with EtOAc (5 mL) and the solution was washed with water (2 mL) and brine (2 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an orange solid which was purified by preparative HPLC (ACN/H_2O/TFA) to afford the desired product (4.6 mg, 15%) as a pale yellow solid. LCMS Anal. Calc'd for $C_{26}H_{28}F_3N_3O_4$ 503.2, found [M+H] 504.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (br. s., 1 H), 7.61 (br. s., 1 H), 7.24 - 7.32 (m, 4 H), 7.16 (d, *J* = 7.83 Hz, 2 H), 6.79 (d, *J* = 8.84 Hz, 2 H), 3.75 (s, 3 H), 3.56 (d, *J* = 17.18 Hz, 1 H), 3.22 - 3.37 (m, 2 H), 3.14 (br. s., 1 H), 2.73 *(d, J* = 17.18 Hz, 1 H), 2.34 (s, 3 H), 2.00 - 2.15 (m, 2 H), 1.70 - 1.80 (m, 2 H), 1.54 (s, 3 H).

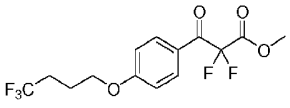
Example 103. *N*-(4-Cyanophenyl)-5,5-difluoro-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxamide

[0350]



Intermediate 103A. Methyl 2,2-difluoro-3-oxo-3-(4-(4,4,4-trifluorobutoxy)phenyl)propanoate

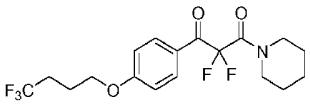
[0351]



[0352] To a solution of Intermediate 14A (3 g, 9.86 mmol) and selectFluor (10.48 g, 29.6 mmol) in acetonitrile (10 mL) was added 1 M methanolic tetrabutylammonium hydroxide (19.72 mL, 19.72 mmol). The reaction mixture was heated to 82 °C for 10 min under microwave conditions. The reaction was diluted with 1:1 ACN and MeOH and filtered rinsing with 1:1 ACN in MeOH (50 mL). The filtrate was evaporated to dryness and the crude product was purified by silica gel chromatography (80 g silica gel, elute with EtOAc in hexanes) to yield the desired product (2.34 g, 69%) as a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 9.08 Hz, 2 H), 6.98 (d, *J* = 9.08 Hz, 2 H), 4.13 (t, *J* = 6.05 Hz, 2 H), 3.93 (s, 3 H), 2.27 - 2.39 (m, 2 H), 2.07 - 2.15 (m, 2 H).

Intermediate 103B. 2,2-Difluoro-1-(piperidin-1-yl)-3-(4-(4,4,4-trifluorobutoxy)phenyl)propane-1,3-dione

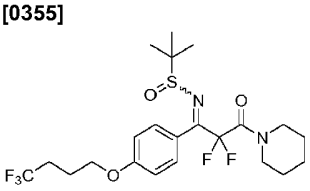
[0353]



[0354] Piperidine (175 µL, 1.763 mmol) was slowly added to Intermediate 103A (500 mg, 1.470 mmol) at rt. The reaction was stirred at rt for 3 h. The reaction was diluted with CH_2Cl_2, loaded onto a 12 g SiO_2 column and eluted with EtOAc in hexanes. Fractions containing the product were combined and evaporated to dryness to provide the product (520 mg, 81%) as a clear oil. LCMS Anal. Calc'd for $C_{18}H_{20}F_5NO_3$ 393.14, found [M+H] 394.2. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, *J* = 9.1 Hz, 2 H), 6.98 - 6.91 (m, 2 H), 4.10 (t, *J* = 5.9 Hz, 2 H), 3.61 - 3.56 (m, 2 H), 3.54 - 3.50 (m, 2 H), 2.39 - 2.26 (m, 2 H), 2.14 - 2.05 (m, 2 H), 1.69 - 1.61 (m, 2 H), 1.60 - 1.51 (m, 4 H).

Intermediate 103C. *N*-(2,2-Difluoro-3-oxo-3-(piperidin-1-yl)-1-(4-(4,4,4-trifluorobutoxy)phenyl)propylidene)-2-methylpropane-2-sulfinamide

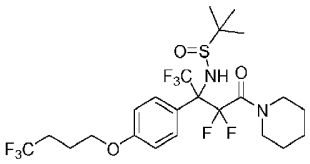
[0355]



[0356] To a solution of Intermediate 103B (1.97 g, 5.01 mmol) and 2-methylpropane-2-sulfinamide (1.821 g, 15.02 mmol) in anhydrous THF (25.04 mL) was added $Ti(OEt)_4$ (5.19 mL, 25.04 mmol). The reaction was heated at refluxed temperature overnight. The reaction was cooled to rt, poured into brine, diluted with EtOAc, and stirred for 30 min. The titanium oxide was removed by filtering through a plug of Celite®. The filtrate layers were separated and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes to yield the desired product (1.62 g, 59%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.80 Hz, 2 H), 6.95 (d, *J* = 9.08 Hz, 2 H), 4.07 (t, *J* = 6.05 Hz, 2 H), 3.62 - 3.69 (m, 1 H), 3.52 - 3.58 (m, 1 H), 3.39 (t, *J* = 5.09 Hz, 2 H), 2.26 - 2.37 (m, 2 H), 2.05 - 2.11 (m, 2 H), 1.53 - 1.70 (m, 7 H), 1.25 (s, 9 H).

Intermediate 103D. 2-Methyl-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-(piperidin-1-yl)-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)propane-2-sulfinamide

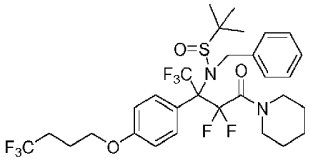
[0357]



[0358] To a solution of TBAT (3.43 g, 6.36 mmol) in DMF (5.89 mL) was added a solution of Intermediate 103C (1.17 g, 2.356 mmol) in THF (5.89 mL). The solution was cooled to 0 °C, and then 2 M $TMSCF_3$ (3.53 mL, 7.07 mmol) in THF was added dropwise. The reaction was stirred at 0 °C for 1 h, and then quenched with brine (20 mL) at 0 °C. The mixture was warmed to rt and diluted with water and EtOAc. The layers were separated. The aqueous layer was washed with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (80 g silica gel, eluted with EtOAc in hexanes) to afford the desired product (773 mg, 58%) as a yellow gum. LCMS Anal. Calc'd for $C_{23}H_{30}F_8N_2O_3S$ 566.18, found [M+H] 567.1. ^1H NMR (500 MHz, CD_3OD) δ 7.69 (d, *J* = 8.53 Hz, 2 H), 6.91 (d, *J* = 9.08 Hz, 2 H), 4.03 (t, *J* = 5.91 Hz, 2 H), 3.50 - 3.62 (m, 2 H), 3.34 - 3.45 (m, 2 H), 2.23 - 2.35 (m, 2 H), 1.98 - 2.07 (m, 2 H), 1.48 - 1.69 (m, 6 H), 1.26 (s, 9 H).

Intermediate 103E. *N*-Benzyl-2-methyl-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-(piperidin-1-yl)-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)propane-2-sulfinamide

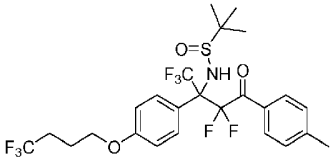
[0359]



[0360] A solution of Intermediate 103D (461 mg, 0.814 mmol) in anhydrous DMF (0.5 mL) was added to a suspension of NaH (65 mg, 1.627 mmol) (60% in mineral oil) at 0 °C. After stirring for 5 min, BnBr (0.484 mL, 4.07 mmol) was added. The reaction mixture was warmed to rt and stirred for 1 h. The reaction was diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (4 g silica gel, eluted with EtOAc in hexanes) to yield the desired product (260 mg, 44%) as a yellow gum. ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.5 Hz, 2 H), 7.33 - 7.27 (m, 3 H), 7.14 (dd, *J* = 7.3, 2.1 Hz, 2 H), 6.80 (d, *J* = 9.1 Hz, 2 H), 4.46 - 4.38 (m, 2 H), 4.00 - 3.95 (m, 2 H), 3.72 (br. s., 1 H), 3.51 (br. s., 1 H), 3.35 - 3.10 (m, 2 H), 2.37 - 2.25 (m, 2 H), 2.09 - 1.99 (m, 2 H), 1.70 - 1.39 (m, 6 H), 1.34 - 1.29 (m, 9 H).

Intermediate 103F. 2-Methyl-*N*-(1,1,1,3,3-pentafluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)propane-2-sulfinamide

[0361]

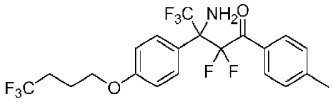


[0362] Mg turnings were suspended in 0.1 N aq HCl for a few minutes, rinsed with water, MeOH and dried under vacuum. A flame dried flask equipped with a stir bar was charged with Mg turnings (0.243 g, 10 mmol), anhydrous THF (4.4 mL) and 4-bromotoluene (1.71 g, 10 mmol) in anhydrous THF (4.4 mL) followed by several drops of 1,2-dibromoethane. The reaction initiated in a few minutes and the mixture became warm. The approximate concentration of the Grignard reagent is 1 M. The

mixture was diluted with 10 mL anhydrous THF to produce a clear solution of *p*-tolylmagnesium bromide (~0.5 M). To a solution of Intermediate 103E (260 mg, 0.396 mmol) in THF (3959 µL) at 0 °C was added the freshly prepared *p*-tolylmagnesium bromide (3959 µL, 1.980 mmol). The reaction was warmed to rt, concentrated to half of the original volume, and stirred for 3 h. The reaction was cooled to 0 °C, quenched with sat'd aq NH_4Cl, and then diluted with EtOAc. The layers were separated and the organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography (24 g silica gel, eluted with EtOAc in hexanes) to afford the desired product (60 mg, 24%) as a yellow gum. ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.55 *(d, J* = 8.5 Hz, 2H), 7.19 *(d, J* = 8.0 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 4.19 (s, 1H), 4.01 (br. s., 2H), 2.40 (s, 3H), 2.31 (dd, *J* = 16.2, 10.2 Hz, 2H), 2.10 - 1.99 (m, 2H), 1.25 (s, 9H).

Intermediate 103G. 3-Amino-2,2,4,4,4-pentafluoro-1-*p*-tolyl-3-(4-(4,4,4-trifluorobutoxy)phenyl)butan-1-one, HCl

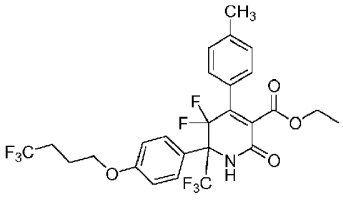
[0363]



[0364] To a solution of Intermediate 103F (30 mg, 0.052 mmol) in MeOH (0.5 mL) was added 4.0 M HCl (0.026 mL, 0.105 mmol) in dioxane. The reaction was stirred at rt for 1 h. The reaction was concentrated and the crude product was used in the next step without further purification. LCMS Anal. Calc'd for $C_{21}H_{19}F_8NO_2$ 469.13, found [M+H] 470.1.

Intermediate 103H. Ethyl 5,5-difluoro-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate

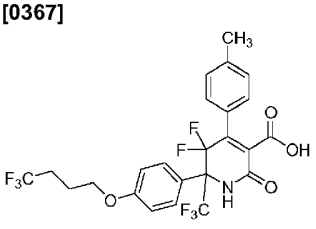
[0365]



[0366] Intermediate 103G (268 mg, 0.530 mmol) was dissolved in MeOH and then passed through $NaHCO_3$ resin (500 mg; 0.9 mmol). The solution was concentrated to yield the free base (230 mg). The free base was dissolved in 9:1 CH_2Cl_2/pyridine (3 mL) added ethyl 3-chloro-3-oxopropanoate (160 mg, 1.060 mmol). The resulting mixture was stirred at rt for 24 h and then concentrated. The residue was taken up with EtOH (1 mL) and treated with piperidine (20 uL). The resulting mixture was stirred at 65 °C for 24 h and then concentrated. The residue was purified by preparative HPLC (MeOH/H_2O/TFA) to yield the desired product (100 mg, 33%) as a foam. LCMS Anal. Calc'd for $C_{26}H_{23}F_8NO_4$ 565.15, found [M+H] 566.1.

Intermediate 103I. 5,5-Difluoro-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid

[0367]



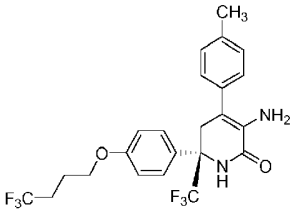
[0368] To a solution of Intermediate 103H (100 mg, 0.177 mmol) in MeOH (2 mL) was added 2 M LiOH (0.4 mL, 0.800 mmol). The resulting mixture was stirred at 100 °C for 15 min. LC-MS indicated the product to be the major component along with a trace amount of SM and 14% of the corresponding methyl ester. 2 M LiOH (100 uL) was then added and the reaction was stirred at 100 °C for an additional 15 min. The reaction was concentrated, acidified with 1 N HCl, and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to yield the desired product (75 mg, 78%) as a solid. LCMS Anal. Calc'd for $C_{24}H_{19}F_8NO_4$ 537.12, found [M+H] 537.9.

Example 103

[0369] To a solution of Intermediate 103I (20 mg, 0.037 mmol) in MeCN (1 mL) was added 3*H*-[1,2,3]triazolo[4,5-*b*]pyridin-3-ol (7.60 mg, 0.056 mmol), 4-aminobenzonitrile (6.59 mg, 0.056 mmol), and EDC (10.70 mg, 0.056 mmol). The resulting mixture was stirred at rt overnight. The reaction mixture was diluted with MeCN and purified by preparative HPLC (MeCN/H_2O/TFA) to yield the desired product (11 mg, 46%) as a solid. LCMS Anal. Calc'd for $C_{31}H_{23}F_8N_3O_3$ 637.16, found [M+H] 637.9. ^1H NMR (500 MHz, CD_3OD) δ 7.67 (d, *J* = 9.08 Hz, 2 H), 7.56 - 7.63 (m, 4 H), 7.22 - 7.26 (m, 2 H), 7.15 - 7.20 (m, 2 H), 7.04 - 7.09 (m, 2 H), 4.12 (t, *J* = 6.05 Hz, 2 H), 2.33 - 2.44 (m, 2 H), 2.30 (s, 3 H), 2.02 - 2.09 (m, 2 H).

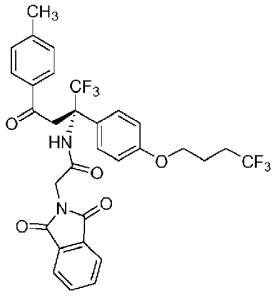
Example 104. (*S*)-3-Amino-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

[0370]



Intermediate 104A. (*S*)-2-(1,3-Dioxoisoindolin-2-yl)-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)acetamide

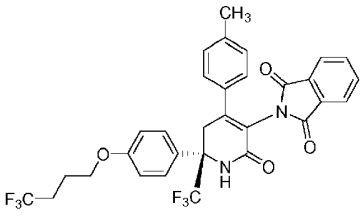
[0371]



[0372] To a solution of 2-(1,3-dioxoisoindolin-2-yl)acetic acid (592 mg, 2.88 mmol) in dry DCM (10 mL) was added PPh_3 (2269 mg, 8.65 mmol) fairy rapidly, and then CCl_3CN (500 mg, 3.46 mmol) was added dropwise. The mixture was stirred at rt for 3 h and a solution of Intermediate 2F, isomer 2 (500 mg, 1.15 mmol) in dry DCM (3 mL), followed by pyridine (0.3 mL) were added. The mixture was stirred at rt overnight. The mixture was diluted with DCM (10 mL) and washed with sat'd $NaHCO_3$ (2 × 8 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography to yield the desired product (620 mg, 87%). LCMS Anal. Calc'd for $C_{31}H_{26}F_6N_2O_5$ 620.17, found [M+H] 621.3.

Intermediate 104B. (*S*)-2-(2-Oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)isoindoline-1,3-dione

[0373]



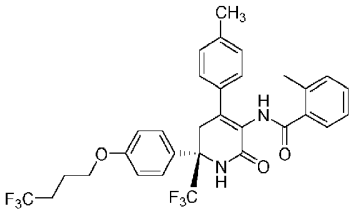
[0374] Intermediate 104A (145 mg, 0.234 mmol) was dissolved in MeOH (2.2 mL) and then 1 N NaOH (0.2 mL) was added. The mixture was stirred at 69 °C for 45 min and added another 0.2 mL of 1 N NaOH. The reaction was heated at 130 °C under microwave conditions for 10 min. The mixture was neutralized with 1 N HCl and then concentrated. The residue was purified by silica gel chromatography (12 g silica gel, eluted with EtOAc in hexanes) to yield the desired product (80 mg, 57%). LCMS Anal. Calc'd for $C_{31}H_{24}F_6N_2O_4$ 602.16, found [M+H] 603.3.

Example 104

[0375] To a solution of Intermediate 104B (80 mg, 0.133 mmol) in 1 mL of EtOH was added 1 mL of 2 N $MeNH_2$ in MeOH. The mixture was stirred at 67 °C for 24 h. The solvent was removed *in vacuo* and the crude product was purified by silica gel chromatography (4 g silics gel, eluted with EtOAc in hexanes) to yield the desired product (32.3 mg, 52%) as a light brown solid. LCMS Anal. Calc'd for $C_{23}H_{22}F_6N_2O_2$ 472.16, found [M+H] 473.2. ^{1}H NMR (500 MHz, CD_3OD) δ 7.49 (d, *J* = 8.8 Hz, 2 H), 7.31 - 7.17 (m, 4 H), 7.04 - 6.92 (m, 2 H), 4.08 (s, 2 H), 3.46 (d, *J* = 16.2 Hz, 1 H), 3.21 *(d, J* = 16.2 Hz, 1 H), 2.44 - 2.30 (m, 5 H), 2.09 - 1.99 (m, 2 H).

Example 105. (*S*)-2-Methyl-*N*-(2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)benzamide

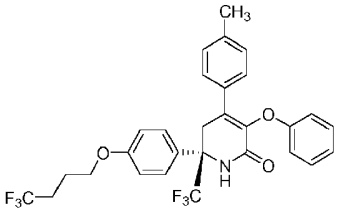
[0376]



[0377] To a solution of 104 (15 mg, 0.032 mmol) in dry DCM (0.5 mL) was added 2-methylbenzoyl chloride (5.4 mg, 0.035 mmol) and pyridine (2.8 µL, 0.035 mmol). The mixture was stirred at rt for 2 h and then concentrated. The residue was purified by preparative HPLC (MeCN/H_2O/TFA) to yield the desired product. LCMS Anal. Calc'd for $C_{31}H_{28}F_6N_2O_3$ 590.20, found [M+H] 591.3. ^{1}H NMR (500 MHz, CD_3OD) δ 7.56 (d, *J* = 8.80 Hz, 2 H), 7.11 - 7.29 (m, 8 H), 6.98 (d, *J* = 9.08 Hz, 2 H), 4.06 (t, *J* = 6.05 Hz, 2 H), 3.73 (d, *J* = 17.06 Hz, 1 H), 3.46 (d, *J* = 16.78 Hz, 1 H), 2.33 (s, 3 H), 2.30 - 2.42 (m, 2 H), 2.22 (s, 3 H), 1.98 - 2.06 (m, 2 H).

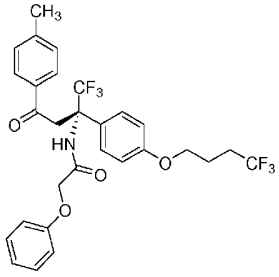
Example 106. (*S*)-3-Phenoxy-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-one

[0378]



Intermediate 106A. (*S*)-2-Phenoxy-*N*-(1,1,1-trifluoro-4-oxo-4-*p*-tolyl-2-(4-(4,4,4-trifluorobutoxy)phenyl)butan-2-yl)acetamide

[0379]

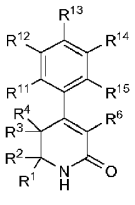


[0380] To a mixture of triphenylphosphine (138 mg, 0.318 mmol) in dry DCM (0.8 mL) was added 2-phenoxyacetic acid (26 mg, 0.173 mmol), followed by trichloroacetonitrile (30 mg, 0.208 mmol). The mixture was stirred at rt for 2.5 h. To the mixture was added a solution of Intermediate 2F, isomer 2 (30 mg, 0.069 mmol) in dry DCM (0.5 mL) followed by pyridine (17 µL, 0.208 mmol). The reaction was stirred at rt overnight. The mixture was concentrated and purified by preparative HPLC (MeOH/H_2O/TFA) to yield the desired product (27 mg, 69%) as a brown oil. LCMS Anal. Calc'd for $C_{29}H_{27}F_6NO_4$ 567.18, found [M+H] 568.3.

Example 106

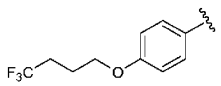
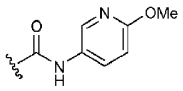
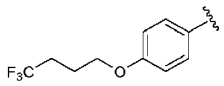
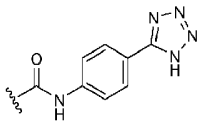
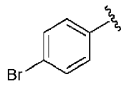
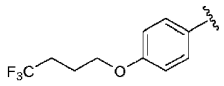
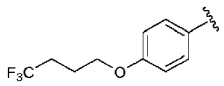
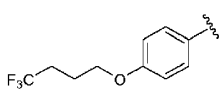
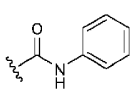
[0381] To a solution of Intermediate 106A (26 mg, 0.046 mmol) in MeOH (0.5 mL) was added 1 N NaOH (60 µL). The mixture was heated at 130 °C under microwave conditions for 10 min. The mixture was neutralized with 1 N HCl and concentrated. The residue was purified by preparative HPLC (MeCN/H_2O/TFA) to yield the desired product (1.5 mg, 6%) as a light brown oil. LCMS Anal. Calc'd for $C_{29}H_{25}F_6NO_3$ 549.17, found [M+H] 550.3. ^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (d, *J* = 8.80 Hz, 2 H), 7.33 (d, *J* = 8.25 Hz, 2 H), 7.13 (d, *J* = 8.25 Hz, 2 H), 7.01 - 7.08 (m, 4 H), 6.85 - 6.90 (m, 1 H), 6.38 (dd, *J* = 8.67, 0.96 Hz, 2 H), 4.10 - 4.15 (m, 2 H), 3.71 - 3.76 (m, 1 H), 3.61 - 3.67 (m, 1 H), 2.34 - 2.45 (m, 2 H), 2.30 (s, 3 H), 2.02 - 2.11 (m, 2 H).

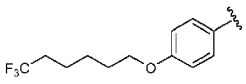
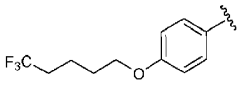
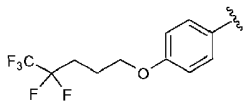
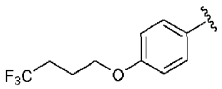
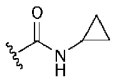
[0382] Examples 110-273 expressed by Formula (II), unless noted in the table, may be made by one skilled in the art by appropriate application of the procedures described for Examples 1-16 and Examples 102-. R^{11} to R^{15} are hydrogen, unless noted in the table.

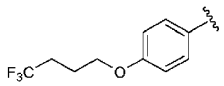
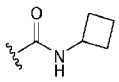
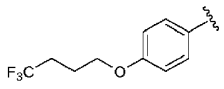
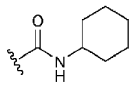
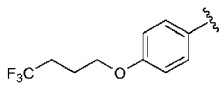
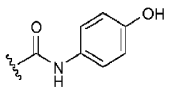
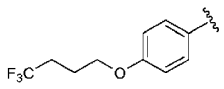


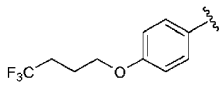
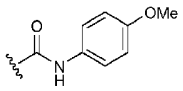
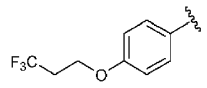
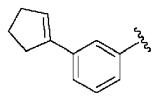
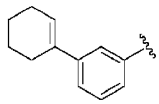
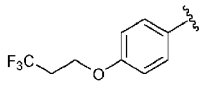
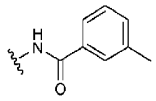
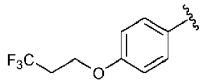
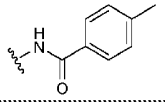
(II)

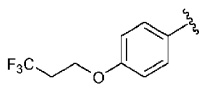
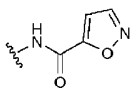
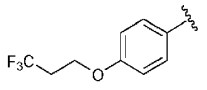
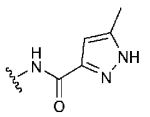
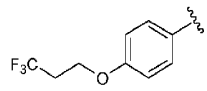
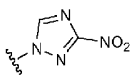
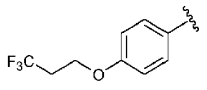
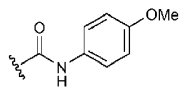
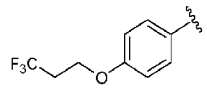
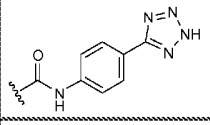
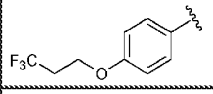
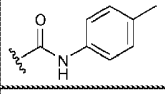
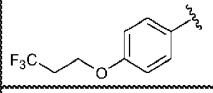
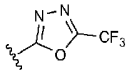
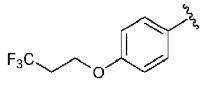
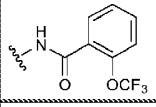
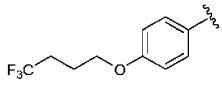
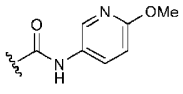
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)

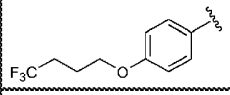
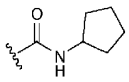
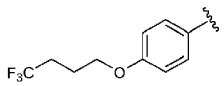
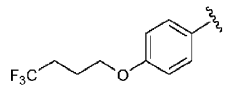
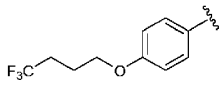
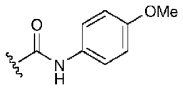
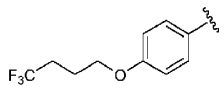
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
110 S-isomer		CF_3	H		$R^{13} = CH_3$	608.1	8.13 (d, *J*= 2.5 Hz, 1H), 7.93 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.46 (d, *J* = 9.1 Hz, 2H), 7.22 (s, 1H), 7.20 - 7.15 (m, 2H), 7.13 - 7.08 (m, 2H), 6.94 (d, *J* = 9.1 Hz, 2H), 6.67 (d, *J* = 9.1 Hz, 1H), 4.02 (t, *J* = 5.9 Hz, 2H), 3.90 (br. s., 3H), 3.56 - 3.38 (m, 2H), 2.39 - 2.25 (m, 5H), 2.10 - 2.01 (m, 2H).
111 S-isomer		CF_3	H		$R^{13} = CH_3$	645.2	7.88 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 7.7 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.75 - 3.46 (m, 2H), 2.43 - 2.32 (m, 2H), 2.29 (s, 3H), 2.11 - 1.97 (m, 2H).
112 Rac		CF_3	H		$R^{13} = CH_3$	480.0	
113 S-isomer		CF_3	H		$R^{13} = CH_3$	526.1	9.07 (d, *J* = 1.1 Hz, 1H), 7.63 *(d, J* = 8.5 Hz, 2H), *7.16-7.09(m,J=8.0Hz,* 2H), 7.09 - 7.03 (m, 2H), 6.93 - 6.86 (d, *J* = 7.7 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 4.00 (s, 1H), 3.92 (d, *J* = 17.6 Hz, 1H), 3.77 *(d, J* = 17.6 Hz, 1H), 2.46 - 2.34 (m, 2H), 2.30 (s, 3H), 2.12 - 2.02 (m, 2H).
114 S-isomer		CF_3	H		$R^{13} = CH_3$	524.1	
115 S-isomer		CF_3	H		$R^{13} = CH_3$	577.2	

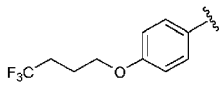
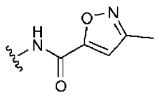
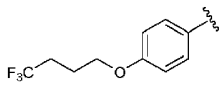
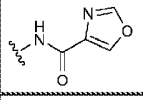
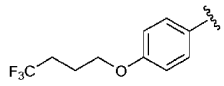
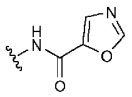
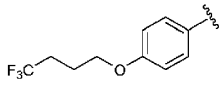
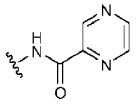
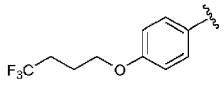
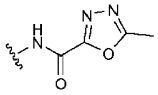
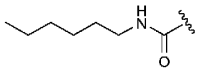
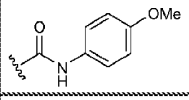
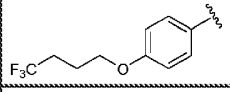
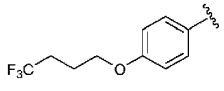
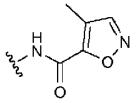
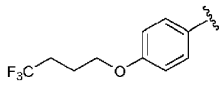
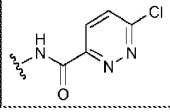
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
116 Rac		CF_3	H		$R^{13} = CH_3$	554.2	7.42 *(d, J* = 8.5 Hz, 2H), 7.16 *(d, J* = 8.0 Hz, 2H), 7.10 (br. s., 1H), 6.95 (dd, *J* = 15.0, 8.4 Hz, 4H), 3.97 (t, *J* = 6.3 Hz, 2H), 3.59 (d, *J* = 5.5 Hz, 2H), 2.36 (s, 3H), 2.16 - 2.04 (m, 2H), 1.86 - 1.77 (m, 2H), 1.69 - 1.59 (m, 2H), 1.59 - 1.50 (m, 2H), 0.93 - 0.79 (m, 3H)
117 Rac		CF_3	H		$R^{13} = CH_3$	540.1	7.43 *(d, J* = 8.5 Hz, 2H), 7.17 (d, *J* = 7.7 Hz, 2H), 7.03 - 6.91 (m, 5H), 3.99 (t, *J* = 5.9 Hz, 2H), 3.65 - 3.53 (m, 2H), 2.37 (s, 3H), 2.23 - 2.11 (m, 2H), 1.92 - 1.82 (m, 2H), 1.82 - 1.72 (m, 2H)
118 Rac		CF_3	H		$R^{13} = CH_3$	576.1	7.44 *(d, J* = 8.5 Hz, 2H), 7.17 *(d, J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 11.4, 8.7 Hz, 4H), 6.80 (br. s., 1H), 4.07 - 4.01 (m, 2H), 3.59 (d, *J* = 7.4 Hz, 2H), 2.37 (s, 3H), 2.33 - 2.19 (m, 2H), 2.10 (dd, *J* = 9.5, 5.6 Hz, 2H)
119 S-isomer		CF_3	H		$R^{13} = CH_3$	541.2	7.44 *(d, J* = 8.3 Hz, 2H), 7.21 - 7.16 (m, 2H), 7.14 -7.09 (m, 2H), 6.96 *(d, J* = 8.8 Hz, 2H), 4.06 (t, *J* = 5.9 Hz, 3H), 3.58 - 3.27 (m, 2H), 2.48 - 2.27 (m, 5H), 2.09 (dd, *J* = 9.5, 5.9 Hz, 2H), 0.97 - 0.80 (m, 2H), 0.75 - 0.61 (m, 2H), 0.38 (d, *J* = 3.6 Hz, 2H)

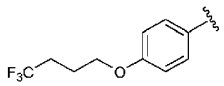
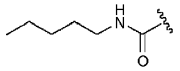
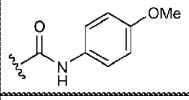
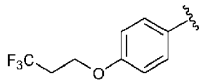
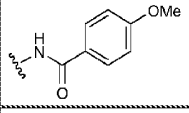
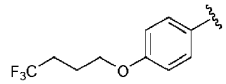
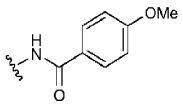
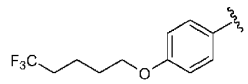
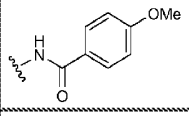
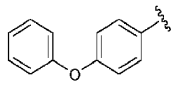
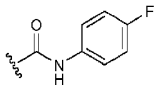
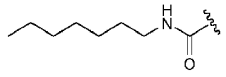
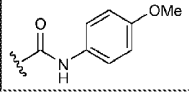
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
120 S-isomer		CF_3	H		$R^{13} = CH_3$	555.2	7.43 (d, *J* = 8.5 Hz, 2H), 7.20 - 7.03 (m, 5H), 6.97 - 6.88 (m, 2H), 4.36 - 4.22 (m, 1H), 4.08 - 3.98 (m, 2H), 3.53 - 3.27 (m, 2H), 2.44 - 2.16 (m, 8H), 2.12 - 2.02 (m, 2H), 1.78 - 1.51 (m, 4H)
121 S-isomer		CF_3	H		$R^{13} = CH_3$	583.3	7.49 - 7.37 (m, 2H), 7.22 - 7.07 (m, 4H), 6.97 - 6.84 (m, 3H), 6.74 *(d, J* = 8.0 Hz, 1H), 4.10 - 3.95 (m, 3H), 3.77 - 3.62 (m, 1H), 3.52 - 3.26 (m, 2H), 2.42 - 2.25 (m, 6H), 2.15 - 1.96 (m, 3H), 1.86 - 1.64 (m, 2H), 1.64 - 1.44 (m, 4H), 1.35 - 1.16 (m, 3H), 1.14 - 0.93 (m, 4H)
122 S-isomer		CF_3	H		$R^{13} = CH_3$	593.3	7.55 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.14 - 7.09 *(d, J* = 8.8 Hz, 2H), 7.02 - 6.97 (d, *J* = 8.8 Hz, 2H), 6.68 - 6.62 (m, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.67 *(d, J*= 17.1 Hz, 1H), 3.51 (d, *J* = 17.1 Hz, 1H), 2.45 - 2.35 (m, 2H), 2.34 (s, 3H), 2.09 - 2.00 (m, 2H).
123 S-isomer		CF_3	H		$R^{13} = CH_3$	515.2	7.57 - 7.50 (m, *J* = 8.8 Hz, 2H), 7.27 - 7.23 (m, *J* = 8.3 Hz, 2H), 7.23 - 7.19 (m, *J* = 8.3 Hz, 2H), 7.02 - 6.97 (m, *J* = 9.1 Hz, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.60 (d, *J* = 17.1 Hz, 1H), 3.46 *(d, J* = 17.1 Hz, 1H), 2.57 (s, 3H), 2.45 - 2.37 (m, 2H), 2.36 (s, 3H), 2.11 - 1.99 (m, 2H).

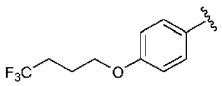
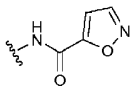
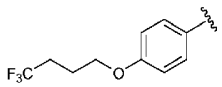
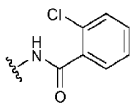
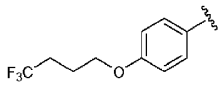
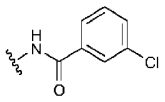
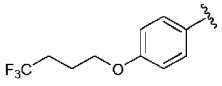
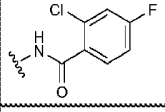
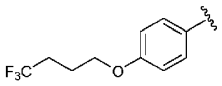
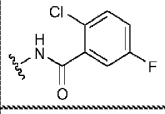
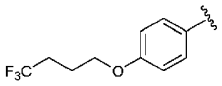
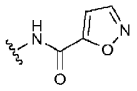
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
124 Rac		CF_3	F		$R^{13} = CH_3$	643.3	7.90 (s, 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.17 (m, 6H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.95 (br. s., 1H), 6.78 (d, *J* = 9.1 Hz, 2H), 4.05 (t, *J* = 5.9 Hz, 2H), 3.81 - 3.71 (m, 3H), 2.44 - 2.27 (m,5H), 2.13-2.03 (m, 2H)
125 Rac		CF_3	H		$R^{13} = CH_3$	512.1	7.45 (d, *J* = 8.5 Hz, 3H), 7.13 (d, *J* = 7.7 Hz, 2H), 6.93 (d, *J* = 7.7 Hz, 4H), 4.18 (t, *J* = 6.5 Hz, 2H), 3.68 - 3.52 (m, 2H), 2.67 - 2.56 (m, 2H)
126 Rac		CF_3	H		$R^{13} = CH_3$	466.2	
127 Rac		CF_3	H		$R^{13} = CH_3$	480.1	7.50 - 7.40 (m, 4H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.09 (br. S., 1H), 6.98 (d, *J* = 7.7 Hz, 2H), 6.17 (br. s., 1H), 2.36 (s, 5H), 2.21 (d, *J* = 3.6 Hz, 2H), 1.82 - 1.74 (m, 2H), 1.70 - 1.62 (m, 2H)
128 S-isomer		CF_3	H		$R^{13} = CH_3$	591.3	
129 S-isomer		CF_3	H		$R^{13} = CH_3$	591.3	

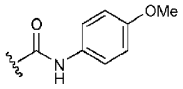
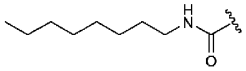
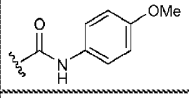
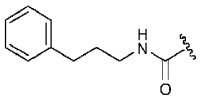
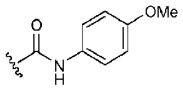
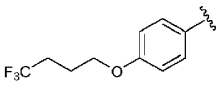
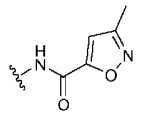
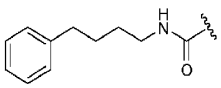
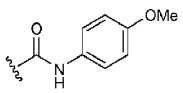
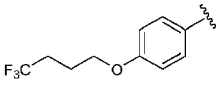
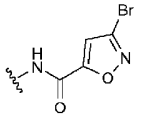
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
130 S-isomer		CF_3	H		$R^{13} = CH_3$	568.2	8.47 (d, *J* = 1.9 Hz, 1H), 7.61 - 7.54 (ab quartet, *J* = 8.8 Hz, 2H), 7.24 - 7.20 (ab quartet, *J* = 8.3 Hz, 2H), 7.19 - 7.15 (ab quartet, *J* = 8.3 Hz, 2H), 7.04 - 6.98 (m, 2H), 6.93 - 6.87 (m, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.75 *(d, J*= 17.1 Hz, 1H), 3.51 (d, *J* = 16.8 Hz, 1H), 2.46 - 2.34 (m, 2H), 2.32 (s, 3H), 2.12 - 2.01 (m, 3H).
131 S-isomer		CF_3	H		$R^{13} = CH_3$	581.3	
132 S-isomer		CF_3	H		$R^{13} = CH_3$	570.2	
133 Rac		CF_3	F		$R^{13} = CH_3$	643.1	8.07 (br. s., 1H), 7.63 (d, *J*= 8.8 Hz, 2H), 7.24 - 7.15 (m, 6H), 6.96 (d, *J* = 9.1 Hz, 2H), 6.76 *(d, J* = 8.8 Hz, 2H), 4.09 - 3.97 (m, 2H), 3.75 (s, 3H), 2.39 - 2.25 (m, 5H), 2.12 - 2.02 (m, 2H)
134 Rac		CF_3	F		$R^{13} = CH_3$	680.9	
135 Rac		CF_3	F		$R^{13} = CH_3$	626.9	
136 S-isomer		CF_3	H		$R^{13} = CH_3$	594.1	
137 S-isomer		CF_3	H		$R^{13} = CH_3$	661.1	
140 Rac		CF_3	F		$R^{13} = CH_3$	643.9	

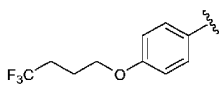
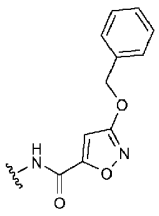
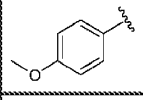
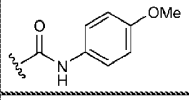
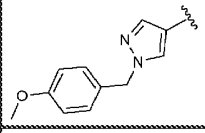
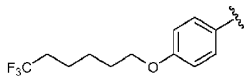
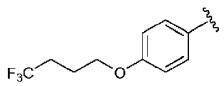
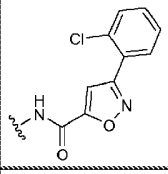
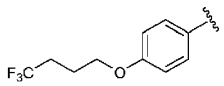
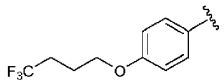
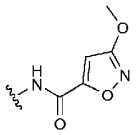
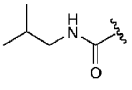
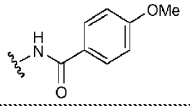
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
141 Rac		CF_3	F		$R^{13} = CH_3$	604.9	
142 S-isomer		CF_3	H		R^{11} = F R^{13} = OCH_3	560.1	9.17 (s, 1H), 7.59 (d, J = 8.8 Hz, 2H), 7.07 - 7.00 (m, 2H), 6.95 (t, J = 8.5 Hz, 1H), 6.69 (dd, J = 8.8, 2.5 Hz, 1H), 6.63 (dd, J = 12.7, 2.5 Hz, 1H), 4.09 (t, J = 6.1 Hz, 2H), 3.90 - 3.81 (m, 1 H), 3.76 (s, 3H), 3.74 - 3.66 (m, 1H), 2.47 - 2.30 (m, 2H), 2.12 - 1.94 (m, 2H).
143 S-isomer		CF_3	H		$R^{13} = OCH_3$	542.1	9.05 (s, 1H), 7.60 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 9.1 Hz, 2H), 6.97 - 6.88 (m, 1H), 6.86 - 6.76 (m, 1H), 4.09 (t, J = 6.1 Hz, 2H), 3.92 - 3.70 (m, 2H), 3.75 (S, 3H), 2.45 - 2.29 (m, 2H), 2.10 - 1.94 (m, 2H).
148 S-isomer		CF_3	H		$R^{11} = CH_3$ R_{13} = CH_3	621.2	7.49 - 7.41 (m, 2H), 7.35 (d, *J* = *8.0* Hz, 2H), 7.03 - 6.65 (m, 7H), 4.07 - 3.99 (m, 2H), 3.71 (s, 3H), 3.51 - 3.42 (m, 1H), 3.28 - 3.14 (m, 1H), 2.38 - 2.21 (m, 8H), 2.11 - 1.99 (m, 2H).
149 S-isomer		CF_3	H		$R^{13} = OCHF_2$	578.1	□□09.09 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.08 - 7.03 (m, 6H), 6.97 - 6.68 (m, 1H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.92 (d, *J* = 17.9 Hz, 1H), 3.77 (d, *J* = 17.9 Hz, 1H), 2.43 - 2.31 (m, 2H), 2.10 - 1.98 (m, 2H).

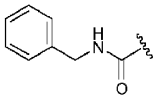
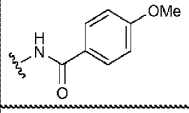
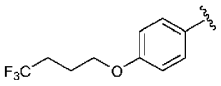
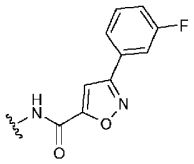
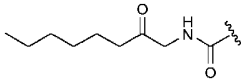
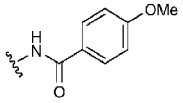
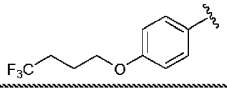
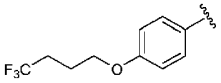
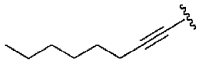
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
150 S-isomer		CF_3	F		$R^{13} = CH_3$	582.2	7.54 (d, *J* = 8.8 Hz, 2H), 7.23 - 7.11 (m, 4H), 7.03 - 6.94 (m, 2H), 6.71 (s, 1H), 4.06 (t, *J* = *6.1* Hz, 2H), 3.98 (s, 1H), 3.71 (d, *J*= 17.1 Hz, 1H), 3.47 *(d, J* = 16.8 Hz, 1H), 2.45 - 2.31 (m, 2H), 2.29 (d, *J* = 6.3 Hz, 6H), 2.12 - 1.96 (m, 2H).
151 S-isomer		CF_3	H		$R^{13} = CH_3$	568.2	
152 S-isomer		CF_3	H		$R^{13} = CH_3$	568.2	
153 S-isomer		CF_3	H		$R^{13} = CH_3$	579.2	
154 S-isomer		CF_3	H		$R^{13} = CH_3$	583.1	7.58 - 7.49 (ab quartet, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.03 - 6.92 (m, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.72 (d, *J* = 17.3 Hz, 1H), 3.49 (d, *J* = 17.1 Hz, 1H), 2.55 (s, 3H), 2.43 - 2.33 (m, 2H), 2.30 (s, 3H), 2.09 - 1.97 (m, 2H).
155 Rac		CH_3	H		$R^{13} = CH_3$	478.4	
156 S-isomer		CF_3	H		$R^{11} = CH_3$ $R^{13} = CH_3$	540.1	
157 S-isomer		CF_3	H		$R^{13} = CH_3$	582.2	
158 S-isomer		CF_3	H		$R^{13} = CH_3$	613.2	

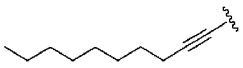
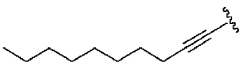
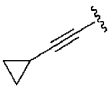
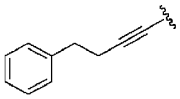
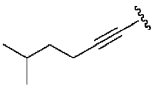
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
159 Rac		CF_3	F		$R^{13} = CH_3$	562.2	
161 Rac		CH_3	H		$R^{13} = CH_3$	464.3	
162 Rac		CF_3	F		$R^{13} = CH_3$	628.9	
163 Rac		CF_3	F		$R^{13} = CH_3$	656.9	8.05 (s, 1H), 7.61 *(d, J*= 8.8 Hz, 2H), 7.25 - 7.16 (m, 6H), 7.02 - 6.94 (m, 2H), 6.82 - 6.73 (m, 2H), 6.60 (br. s., 1H), 4.01 (td, *J* = 6.1, 1.4 Hz, 2H), 3.75 (s, 3H), 2.35 (s, 3H), 2.24 - 2.10 (m, 2H), 1.93 - 1.85 (m, 2H), 1.83 - 1.74 (m, 2H), 1.67 (br. s., 3H)
164 Rac		CF_3	F		$R^{13} = CH_3$	671.0	
165 S-isomer		CF_3	H		$R^{13} = CH_3$	561.2	7.59 (d, *J* = 8.8 Hz, 2H), 7.42 - 7.36 (m, 2H), 7.35 - 7.28 (m, 4H), 7.20 - 7.16 (m, 3H), 7.06 - 6.99 (m, 4H), 6.98 - 6.93 (m, 2H), 3.66 (d, *J* = 17.3 Hz, 1H), 3.52 *(d, J* = 17.3 Hz, 1H), 2.30 (s, 3H).
166 Rac		CH_3	H		$R^{13} = CH_3$	492.2	

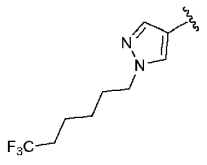
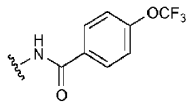
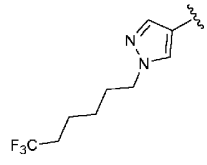
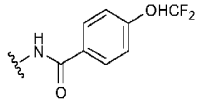
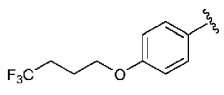
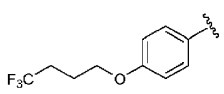
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
167 S-isomer		CF_3	H		$R^{13} = OHCF_2$	620.2	8.38 (d, *J* = 1.7 Hz, 1H), 7.61 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.34 - 7.24 (m, 2H), 7.13 - 7.04 (ab quartet, *J* = 8.8 Hz, 2H), 6.99 - 6.92 (m, 2H), 6.86 (s, 1H), 4.26 (br. s., 1H), 4.05 (t, *J*= 5.9 Hz, 2H), 3.69 *(d, J* = 17.1 Hz, 1H), 3.42 *(d, J* = 17.1 Hz, 1H), 2.41 - 2.27 (m, 2H), 2.10 - 1.97 (m, 2H).
168 S-isomer		CF_3	H		$R^{13} = CH_3$	611.2	
169 S-isomer		CF_3	H		$R^{13} = CH_3$	611.2	
170 S-isomer		CF_3	H		$R^{13} = CH_3$	629.2	
171 S-isomer		CF_3	H		$R^{13} = CH_3$	629.3	
172 S-isomer		CF_3	H		$R^{13} = OCH_3$	584.2	8.37 (d, *J* = 1.7 Hz, 1H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.28 - 7.17 (m, 2H), 6.99 - 6.91 (m, 2H), 6.89 - 6.82 (m, 3H), 4.05 (t, *J* = 6.1 Hz, 2H), 3.78 (s, 3H), 3.68 *(d, J* = 16.8 Hz, 1H), 3.42 (d, *J* = 17.1 Hz, 1H), 2.45 - 2.23 (m, 2H), 2.10 - 1.98 (m, 2H).

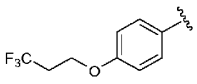
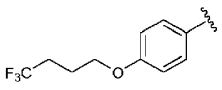
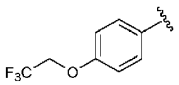
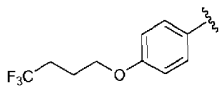
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
173 Rac		CH_3	H		$R^{13} = CH_3$	618.4	7.34 (d, *J* = 8.0 Hz, 2H), 7.26 (d, *J* = 9.1 Hz, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.79 (d, *J* = 9.1 Hz, 2H), 3.76 (s, 3H), 3.43 - 3.37 *(d, J* = 17.5 Hz, 1H), 3.22 *(t, J* = 7.1 Hz, 2H), 2.86 - 2.80 (d, *J* = 17.2 Hz, 1H), 2.32 (s, 3H), 1.53 (s, 3H), 1.31 - 1.21 (m, 28H), 0.88 (t, *J* = 7.1 Hz, 3H)
174 Rac		CH_3	H		$R^{13} = CH_3$	506.4	
175 Rac		CH_3	H		$R^{13} = CH_3$	512.4	
176 S-isomer		CF_3	H		$R^{13} = OCH_3$	598.2	7.54 (d, *J* = 8.8 Hz, 2H), 7.32 - 7.23 (m, 2H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.88 *(d, J* = 8.8 Hz, 2H), 6.73 (s, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.71 (d, *J* = 17.1 Hz, 1H), 3.49 *(d, J* = 17.1 Hz, 1H), 2.45 - 2.32 (m, 2H), 2.31 - 2.26 (m, 3H), 2.08 - 1.97 (m, 2H).
178 Rac		CH_3	H		$R^{13} = CH_3$	526.4	
179 S-isomer		CF_3	H		$R^{13} = CH_3$	648.2	7.54 (d, *J* = 8.8 Hz, 2H), 7.23 - 7.11 (m, 4H), 7.03 - 6.93 (m, 3H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.72 *(d, J* = 16.9 Hz, 1H), 3.48 *(d, J* = 17.2 Hz, 1H), 2.44 - 2.32 (m, 2H), 2.30 (s, 3H), 2.08 - 1.97 (m, 2H).

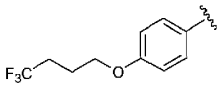
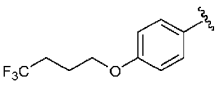
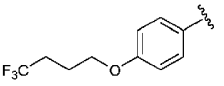
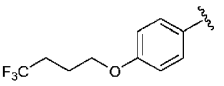
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
180 S-isomer		CF_3	H		$R^{13} = CH_3$	674.3	
181 Rac		CF_3	F		$R^{13} = CH_3$	547.0	
182 Rac		CF_3	H		$R^{13} = CH_3$	510.3	
183 Rac S-isomer		CF_3	H		$R^{13} = CH_3$	554.3	7.57 - 7.48 (m, 2H), 7.13 - 7.05 (m, 2H), 7.02 - 6.94 (m, 2H), 6.88 - 6.77 (m, 2H), 4.07 - 3.99 (m, 2H), 2.29 (s, 3H), 2.19 - 2.07 (m, 2H), 1.89 - 1.78 (m, 2H), 1.69 - 1.55 (m, 4H)
185 S-isomer		CF_3	H		$R^{13} = CH_3$	678.3	
186 S-isomer		CF_3	H		$R^{13} = CH_3$	540.3	
187 S-isomer		CF_3	H		$R^{13} = CH_3$	598.3	7.57 - 7.50 (m, *J* = 8.8 Hz, 2H), 7.21 - 7.12 (m, 4H), 7.01 - 6.94 (m, 2H), 6.48 (s, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.95 (s, 3H), 3.71 *(d, J* = 17.1 Hz, 1H), 3.47 *(d, J* = 17.1 Hz, 1H), 2.44 - 2.32 (m, 2H), 2.30 (s, 3H), 2.07 - 1.98 (m, 2H).
188 Rac		CH_3	H		$R^{13} = CH_3$	450.1	

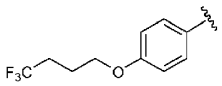
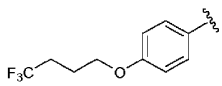
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
189 Rac		CH_3	H		$R^{13} = CH_3$	484.1	
190 S-isomer		CF_3	H		$R^{13} = CH_3$	662.3	
191 Rac		CH_3	H		$R^{13} = CH_3$	520.2	
192 S-isomer		CF_3	H		$R^{13} = CH_3$	526.3	
193 S-isomer		CF_3	H		$R^{13} = OCH_3$	542.1	1H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.65 (s, 1H), 7.54 *(d, J*= 8.4 Hz, 2H), 6.98 (d, *J*= 8.6 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.79 *(d, J* = 8.4 Hz, 2H), 4.07 (t, *J*= 6.0 Hz, 2H), 3.77 (s, 3H), 3.69 *(d, J*= 17.7 Hz, 1H), 3.60 (d, *J* = 17.7 Hz, 1 H), 2.41 - 2.28 (m, 2H), 2.06 (dq, *J* = 12.1, 6.3 Hz, 2H).
194 Rac		CF_3	H		$R^{13} = CH_3$	432.3	7.21 *(d, J* = 7.9 Hz, 2H), 7.08 *(d, J* = 8.1 Hz, 2H), 6.25 (s, 1H), 3.39 (d, *J* = 18.5 Hz, 1H), 3.34 (d, *J* = 18.9 Hz, 1H), 2.39 (s, 3H), 2.23 (t, *J* = 7.2 Hz, 2H), 1.55 - 1.47 (m, 2H), 1.40 - 1.23 (m, 6H), 0.87 (t, *J* = 6.9 Hz, 3H).

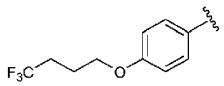
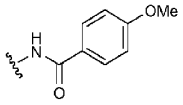
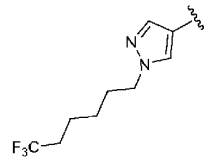
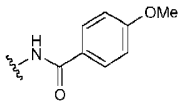
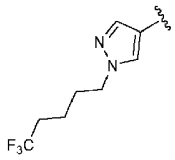
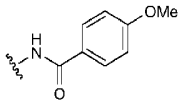
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
195 Rac		CF_3	H		$R^{13} = CH_3$	460.4	7.21 (d, *J*= 7.9 Hz, 2H), 7.08 (d, *J*= 8.1 Hz, 2H), 6.32 (s, 1H), 3.37 (AB quartet, *J* = 18.7 Hz, 2H), 2.39 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.51 (quin, *J* = 7.2 Hz, 2H), 1.39 - 1.20 (m, 10H), 0.91 - 0.84 (m, 3H).
196 R-isomer		CF_3	H		$R^{13} = CH_3$	460.4	7.17 (d, *J* = 7.9 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.74 (s, 1H), 3.43 - 3.32 (m, 2H), 2.37 (s, 3H), 2.23 *(t, J* = 7.0 Hz, 2H), 1.55 - 1.47 (m, 2H), 1.37 - 1.22 (m, 10H).
197 S-isomer		CF_3	H		$R^{13} = CH_3$	388.3	7.20 (d, *J* = 7.9 Hz, 2H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.34 (s, 1H), 3.38, 3.32 (ABq, *J* = 18.9 Hz, 2H), 2.39 (s, 3H), 1.28 (tt, *J* = 8.3, 5.0 Hz, 1H), 0.89 - 0.83 (m, 2H), 0.76 - 0.71 (m, 2H).
198 S-isomer		CF_3	H		$R^{13} = CH_3$	452.3	7.30 - 7.23 (m, 2H), 7.22 - 7.13 (m, 5H), 6.99 *(d, J* = 8.1 Hz, 2H), 6.57 (s, 1H), 3.33 *(d, J*= 18.9 Hz, 1H), 3.26 *(d, J* = 18.9 Hz, 1H), 2.85 - 2.80 (m, 2H), 2.57 - 2.53 (m, 2H), 2.38 (s, 3H)
199 S-isomer		CF_3	H		$R^{13} = CH_3$	418.3	7.19 (d, *J* = 7.9 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 6.68 (s, 1H), 3.38, 3.35 (ABq, *J* = 18.9 Hz, 2H), 2.37 (s, 3H), 2.24 (t, *J* = 7.4 Hz, 2H), 1.63 (dquin, *J* = 13.4, 6.7 Hz, 1H), 1.41 (q, *J* = 7.3 Hz, 2H), 0.88 (d, *J* = 6.6 Hz, 6H)

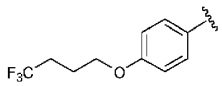
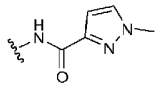
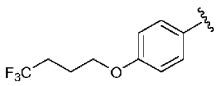
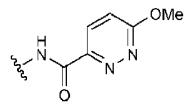
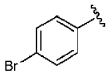
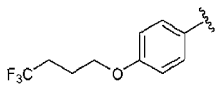
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
200 Rac		CF_3	H		$R^{13} = CH_3$	663.2	9.63 (s, 1H), 7.62 (s, 1H), 7.54 (s, 1H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 2H), 6.87 (s, 1H), 4.13 (t, *J* = 7.2 Hz, 2H), 3.48 (d, *J* = 18.4 Hz, 1H), 3.25 (d, *J* = 18.4 Hz, 1H), 2.42 - 2.31 (m, 3H), 2.08 - 2.03 (m, 2H), 1.96 - 1.85 (m, 2H), 1.62 - 1.53 (m, 2H), 1.41 - 1.31 (m, 2H)
201 Rac		CF_3	H		$R^{13} = CH_3$	645.3	10.16 (s, 1H), 9.00 (s, 1H), 7.99 (s, 1H), 7.70 (s, 1H), 7.51 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 7.12 (t, *J* = 74.3 Hz, 1H), 7.09 *(d, J* = 8.8 Hz, 2H), 4.11 (t, *J* = 6.9 Hz, 2H), 3.41-3.37 (d, *J* = 17.4 Hz, 1H), 3.35 - 3.31 *(d, J* = 17.4 Hz, 1H), 2.28 (s, 3H), 2.23 - 2.17 (m, 2H), 1.85 - 1.75 (m, 2H), 1.52 - 1.44 (m, 2H), 1.31 - 1.22 (m, 2H).
202 S-isomer		CF_3	H		$R^{13} = CH_2OCH_3$	556.3	1HNMR (500 MHz, DMSO-d_6) δ 9.57 (s, 1H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 4.36 (s, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 3.75 (d, *J* = 17.5 Hz, 1H), 3.69 (d, *J* = 17.5 Hz, 1H), 3.27 (s, 3H), 2.48 - 2.37 (m, 2H), 2.01 - 1.89 (m, 2H)
203 S-isomer		CF_3	H		R^{12} = F R^{13} = OCH_2CH_3	574.3	

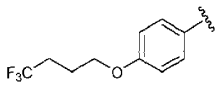
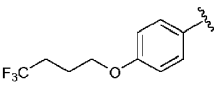
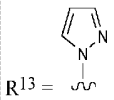
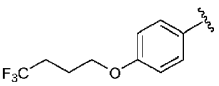
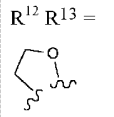
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
204 S-isomer		CF_3	H		$R^{13} = CH_3$	512.1	1H NMR (500 MHz, MeOD:$CDCl_3$ (1:1)) δ 7.61 (s, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 6.97 (dd, *J* = 10.4, 8.3 Hz, 4H), 6.84 (d, *J* = 8.1 Hz, 2H), 4.24 (t, *J* = 6.4 Hz, 2H), 3.71 (d, *J* = 17.2 Hz, 1H), 3.50 *(d, J*= 17.2 Hz, 1H), 3.08 - 3.03 (m, 4H), 2.67 (qt, *J* = 10.8, 6.3 Hz, 2H), 1.78 (dq, *J* = 11.3, 5.5 Hz, 4H), 1.69 (q, *J* = 5.9 Hz, 2H).
205 S-isomer		CF_3	H		$R^{13} = OCHF_2$	578.1	1H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.61 (s, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.05 - 6.96 (m, 5H), 6.66 (t, *J* = 73.4 Hz, 1H), 4.07 (t, *J* = 6.0 Hz, 2H), 3.70 (d, *J* = 17.9 Hz, 1H), 3.57 *(d, J*= 17.8 Hz, 1H), 2.41 - 2.28 (m, 2H), 2.11 - 2.02 (m, 2H).
206 S-isomer		CF_3	H		$R^{13} = CH_3$	498.1	1H NMR (500 MHz, MeOD-$CDCl_3$ (1:1)) δ 7.60 - 7.57 (m, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.48 (q, *J* = 8.2 Hz, 1H), 3.70 (d, *J* = 17.8 Hz, 1H), 3.58 (d, *J* = 17.8 Hz, 1H), 2.30 (s, 1H).
207 S-isomer		CF_3	H		R^{12} R^{13} = 	562.1	1H NMR (500 MHz, $CDCl_3$: MeOD (1:1)) δ 7.81 - 7.73 (m, 2H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.61 (s, 1H), 7.60 - 7.55 (m, 3H), 7.53 - 7.46 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.98 (dd, *J* = 8.5, 1.8 Hz, 1H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.83 (d, *J* = 17.8 Hz, 1H), 3.70 (d, *J* = 17.8 Hz, 1H), 2.41 - 2.28 (m, 2H), 2.11 - 2.01 (m, 2H).

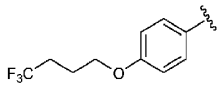
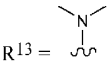
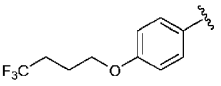
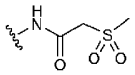
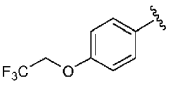
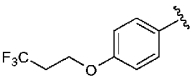
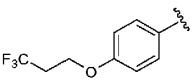
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
208 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	556.1	1H NMR (500 MHz, CDCl3: MeOD (1:1)) δ 7.62 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 4.07 (t, *J* = 6.0 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 3.68 (d, *J* = 17.8 Hz, 1H), 3.59 (d, *J* = 17.7 Hz, 1H), 2.40 - 2.28 (m, 2H), 2.10 - 2.01 (m, 2H), 1.38 (t, *J* = 7.0 Hz, 3H).
209 S-isomer		CF_3	H		R^{12} R^{13} = 	570.2	1H NMR (500 MHz, DMSO-d_6) δ 9.51 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.57 (d, *J* = 2.2 Hz, 1H), 6.41 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.25 - 4.14 (m, 4H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.68 (d, *J* = 18.2 Hz, 1H), 3.63 (d, *J* = 18.5 Hz, 1H), 2.42 (ddd, *J* = 16.4,8.0,5.1 Hz, 2H), 1.93 (dq, *J* = 12.3, 6.4 Hz, 2H).
210 S-isomer		CF_3	H		R^{12} R^{13} = 	566.1	1H NMR (500 MHz, DMSO-d_6) δ 9.42 (s, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.80 (s, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.67 (d, *J* = 17.8 Hz, 1H), 3.60 *(d, J*= 17.9 Hz, 1H), 2.61 (s, 2H), 2.56 (s, 2H), 2.42 (ddd, *J* = 11.4, 8.3, 5.2 Hz, 2H), 1.98 - 1.88 (m, 2H), 1.65 (p, *J* = 2.8 Hz, 4H).
211 S-isomer		CF_3	H		R^{12} R^{13} =	556.2	1H NMR (500 MHz, DMSO-d_6) δ 9.37 (s, 1H), 7.60 (d, *J*

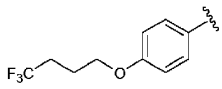
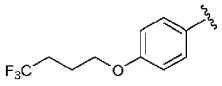
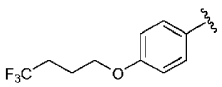
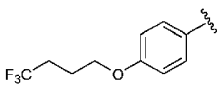
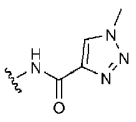
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
							= 8.5 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.57 (s, 1H), 6.48 (d, *J* = 8.1 Hz, 1H), 5.97 (d, *J* = 3.1 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.65 (d, *J* = 17.6 Hz, 1H), *3 .5 8 (d, J* = 17.7 Hz, 1H), 2.46 - 2.35 (m, 2H), 1.93 (dd, *J*= 9.9, 5.4 Hz, 2H).
212 S-isomer		CF_3	H		R^{11} R^{12} =  R^{13} = OCH3	582.3	1H NMR (500 MHz, DMSO-d_6) δ 9.30 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 4.12 - 4.01 (m, 2H), 3.70 (s, 3H), 3.67 (m, 1H), 3.60 *(d, J*= 17.4 Hz, 1H), 2.67 - 2.55 (m, 2H), 2.46 - 2.35 (m, 2H), 2.31 - 2.07 (m, 2H), 1.97 - 1.91 (m, 2H), 1.81 - 1.69 (m, 2H).
213 S-isomer		CHF_2	H		R^{13} = CH_3	508.3	1H NMR (500 MHz, DMSO-d_6) δ 9.10 (s, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 7.9 Hz, 2H), 6.33 (t, *J* = 55.0 Hz, 1H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.57 (d, *J* = 17.9 Hz, 1H), 3.41 (d, *J* = 18.2 Hz, 1 H), 2.44 (ddd, *J* = 11.4, 8.1, 5.2 Hz, 2H), 1.99 - 1.91 (m, 2H).

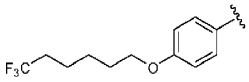
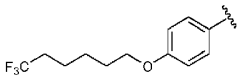
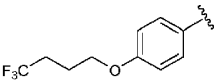
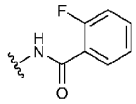
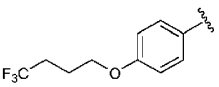
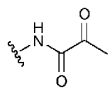
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
214 R-iso mer		H	H		$R^{13} = CH_3$	539.4	1H NMR (500 MHz, DMSO-d_6) δ 9.97 (s, 1H), 8.06 (s, 1H), 7.42 (d, *J* = 8.6 Hz, 2H), 7.36 (dd, *J* = 10.3, 8.2 Hz, 4H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.96 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 4.82 - 4.73 (m, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.83 - 3.72 (m, 1H), 3.71 (s, 3H), 2.88 (qd, *J*= 17.0, 7.6 Hz, 1H), 2.48 - 2.35 (m, 2H), 2.25 (s, 3H), 1.94 (dq, *J* = 12.5, 6.4 Hz, 2H).
228 Rac		CF_3	H		$R^{13} = CH_3$	609.2	7.86 (s, 1H), 7.66 (s, 1H), 7.37 (d, J = 8.25 Hz, 2H), 7.26 (d, J = 9.08 Hz, 2H), 7.21 (d, J = 7.98 Hz, 2H), 6.82 (d, J = 9.08 Hz, 2H), 4.18 (t, J = 6.88 Hz, 2H), 3.76 (s, 3H), 3.58 (d, J = 17.33 Hz, 1H), 3.35 (d, J = 17.33 Hz, 1H), 2.34 (s, 3H), 2.13 (m, 2H), 1.89 (m, 2H), 1.57 (m, 2H), 1.35 (m, 2H).
229 Rac		CF_3	H		$R^{13} = CH_3$	595.2	

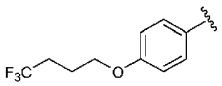
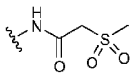
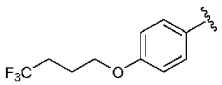
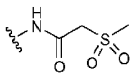
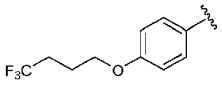
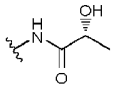
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
231 S-isomer		CF_3	H		$R^{13} = CH_3$	581.4	1H NMR (500 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.23 (s, 1H), 7.54 (d, J = 8.80 Hz, 2H), 7.48 (d, J = 1.65 Hz, 1H), 7.29 (d, J = 7.98 Hz, 2H), 7.15 (d, J = 7.98 Hz, 2H), 7.00 (d, J = 8.80 Hz, 2H), 6.34 (d, J = 1.93 Hz, 1H), 4.07 (t, J = 6.05 Hz, 2H), 3.67 (s, 3H), 3.48 (d, J = 17.06 Hz, 1H), 3.39 (d, J = 17.06 Hz, 1H), 2.43 (m, 2H), 2.27 (s, 3H), 1.95 (m, 2H).
232 S-isomer		CF_3	H		$R^{13} = CH_3$	609.1	8.13 (d, J = 9.63 Hz, 1H), 7.54 (d, J = 8.80 Hz, 2H), 7.26 (d, J = 8.25 Hz, 2H), 7.23 (d, J = 9.63 Hz, 1H), 7.17 (d, J = 7.99 Hz, 2H), 6.99 (d, J = 9.08 Hz, 2H), 4.07 (t, J = 6.05 Hz, 2H), 4.01 (s, 3H), 3.67 (d, J = 17.33 Hz, 1H), 3.53 (d, J = 17.06 Hz, 1H), 2.37 (m, 2H), 2.29 (s, 3H), 2.03 (m, 2H).
233 S-isomer		CF_3	H		$R^{13} = CH_3$	479.8	
234 S-isomer		CF_3	H		R^{13} - Br	589.9	7.54 (d, *J* = 8.3 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 6.97 (dd, *J* = 8.7, 2.3 Hz, 4H), 6.85 (br. s., 1H), 4.04 (t, *J* = 5.8 Hz, 2H), 3.69 - 3.59 (m, 1H), 3.56 - 3.46 (m, 1H), 2.40 - 2.26 (m, 2H), 2.08 (dd, *J* = 9.4, 6.1 Hz, 2H).

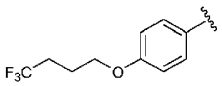
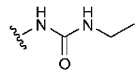
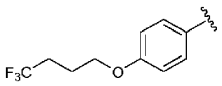
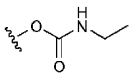
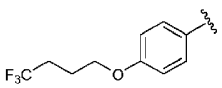
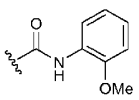
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
235 S-isomer		CF_3	H				1H NMR (500 MHz, DMSO) δ 9.55 (br. s., 1H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.02 *(d,* *J* = 8.8 Hz, 2H), 6.98 - 6.92 (m, 2H), 6.87 (d, *J*= 8.3 Hz, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.80 - 3.61 (m, 2H), 2.46 - 2.29 (m, 2H), 2.00 - 1.90 (m, 2H), 1.89 - 1.79 (m, 1H), 1.00 - 0.88 (m, 2H), 0.69 -0.54 (m, 2H).
236 S-isomer		CF_3	H			578.0	1H NMR (500MHz, DMSO) δ 9.42 (br. s., 1H), 8.47 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 1.1 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.53 (d, *J* = 1.9 Hz, 1H), 4.08 (t, *J* = 6.2 Hz, 2H), 3.78 - 3.63 (m, 2H), 2.46 - 2.34 (m, 2H), 2.02 - 1.86 (m, 2H).
237 S-isomer		CF_3	H			554.0	1H NMR (500MHz, DMSO) δ 9.42 (br. s., 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.02 *(d,* *J* = 8.8 Hz, 2H), 6.97 (s, 1H), 6.68 (d, *J*= 8.5 Hz, 1H), 6.59 (d, *J* = 8.3 Hz, 1H), 4.50 (t, *J* = 8.7 Hz, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.65 (br. s., 2H), 3.06 (t, *J* = 8.7 Hz, 2H), 2.47 - 2.34 (m, 2H), 2.00 - 1.89 (m, 2H).

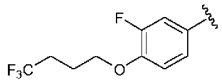
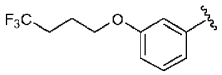
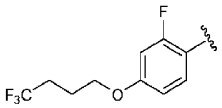
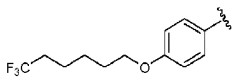
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
238 S-isomer		CF_3	H			555.1	1H NMR (500 MHz, DMSO) δ 9.41 (br. s., 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.84 (d, *J* = 8.5 Hz, 2H), 6.52 (d, *J*= 8.8 Hz, 2H), 4.06 (t, *J* = *5.9* Hz, 2H), 3.75 - 3.55 (m, 2H), 2.89 (s, 6H), 2.42 (dd, *J* = 16.5, 11.0 Hz, 2H), 2.02 - 1.84 (m, 2H).
239 S-isomer		CF_3	H		$R^{13} = CH_3$	593.3	1H NMR (400 MHz, MeOD) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.24 - 7.15 (m, 4H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.97 (s, 2H), 3.67 (d, *J* = 16.9 Hz, 1H), 3.43 (d, *J* = 16.9 Hz, 1H), 2.93 (s, 3H), 2.44 - 2.28 (m, 5H), 2.09 - 1.96 (m, 2H).
240 S-isomer		CF_3	H		$R^{13} = OCH_3$	514.3	1H NMR (400 MHz, MeOD) δ 7.65 (d, *J* = 9.0 Hz, 2H), 7.13 - 7.08 (m, 2H), 6.97 - 6.93 (m, 2H), 6.84 - 6.78 (m, 2H), 4.57 (q, *J* = 8.4 Hz, 2H), 3.75 (s, 3H), 3.72 (d, *J* = 2.4 Hz, 2H).
241 S-isomer		CF_3	H		$R^{13} = OCH_3$	528.3	1H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.25 (t, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.71 (d, *J* = 1.5 Hz, 2H), 2.77 - 2.63 (m, 2H).
242 S-isomer		CF_3	H		$R^{13} = OCF_3$	582.2	1H NMR (400 MHz, MeOD) δ 7.62 (d, *J* = 8.8 Hz, 2H), 7.23 - 7.17 (m, 2H), 7.14 - 7.09 (m, 2H), 7.08 - 7.02 (m, 2H), 4.26 (t, *J* = 6.2 Hz, 2H), 3.83 - 3.66 (m, 2H), 2.77 - 2.63 (m, 2H).

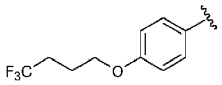
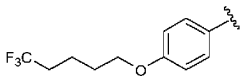
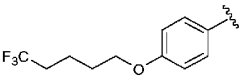
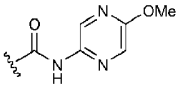
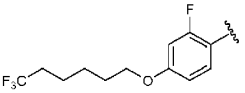
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
243 S-isomer		CF_3	H		$R^{13} = OCF_3$	596.3	1H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.22 - 7.17 (m, 2H), 7.15 - 7.09 (m, 2H), 7.06 - 7.00 (m, 2H), 4.08 (t, *J* = 6.1 Hz, 2H), 3.82 - 3.65 (m, 2H), 2.44 - 2.30 (m, 2H), 2.09 - 1.99 (m, 2H).
244 S-isomer		CF_3	H		$R^{13} = OCH_3$	556.3	1H NMR (400 MHz, MeOD) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.76 (s, 3H), 3.70 *(d, J* = 1.3 Hz, 2H), 2.31 - 2.17 (m, 2H), 1.92 - 1.83 (m, 2H), 1.80-1.70 (m, 2H).
245 S-isomer		CF_3	H		R^{13}= $OCHCF_2$	592.1	1H NMR (400 MHz, MeOD) δ 7.59 (d, *J* = 8.6 Hz, 2H), 7.05 (s, 4H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.87 (t, *J* = 74.6 Hz, 1H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.74, 3.70 (ABq, *J* = 18.0 Hz, 2H), 2.31 - 2.17 (m, 2H), 1.92 - 1.84 (m, 2H), 1.80 - 1.70 (m, 2H)
246 S-isomer		CF_3	H		R^{13} = CH_3	582.3	1H NMR (400 MHz, MeOD) δ 8.18 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.25 - 7.19 (m, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 4.09 (s, 3H), 4.07 - 4.03 (m, 2H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.48 *(d, J* = 16.9 Hz, 1H), 2.44 - 2.31 (m, 2H), 2.28 (s, 3H), 2.08 - 1.98 (m, 2H).

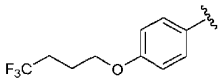
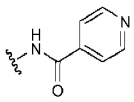
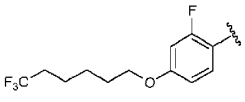
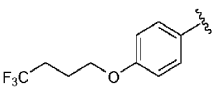
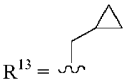
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
247 S-isomer		CF_3	H		$R^{13} = OCH_3$	570.1	1H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 8.8 Hz, 2H), 7.03 - 6.92 (m, 4H), 6.84 - 6.79 (m, 2H), 4.02 (t, *J* = 6.3 Hz, 2H), 3.76 (s, 3H), 3.70 (d, *J* = 1.5 Hz, 2H), 2.25 - 2.11 (m, 2H), 1.87 - 1.77 (m, 2H), 1.69 - 1.53 (m, 4H).
248 S-isomer		CF_3	H		R^{13}= $OCHCF_2$	606.3	1H NMR (400 MHz, MeOD) δ 7.61 (d, *J* = 8.8 Hz, 2H), 7.08 (s, 4H), 7.05 - 7.01 (m, *J* = 9.0 Hz, 2H), 6.90 (t, *J* = 73.7 Hz, 1H), 4.05 (t, *J* = 6.2 Hz, 2H), 3.76, 3.73 (ABq, *J* = 18.5 Hz, 2H), 2.28 - 2.14 (m, 2H), 1.89 - 1.81 (m, 2H), 1.72 - 1.56 (m, 4H)
249 S-isomer		CF_3	H		$R^{13} = CH_3$	595.3	1H NMR (400 MHz, MeOD) δ 7.62 - 7.53 (m, 3H), 7.51 - 7.45 (m, 1H), 7.27 - 7.09 (m, 6H), 7.01 - 6.95 (m, 2H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.71 (d, *J* = 16.9 Hz, 1H), 3.48 (d, *J* = 16.9 Hz, 1H), 2.43 - 2.29 (m, 5H), 2.08 - 1.98 (m, 2H).
250 S-isomer		CF_3	H		$R^{13} = CH_3$	543.4	8.35 (br. s., 1H), 7.44 (d, *J*= 8.8 Hz, 2H), 7.18 - 7.13 (m, 2H), 7.11 - 7.06 (m, 2H), 6.96 - 6.90 (m, 2H), 6.30 (s, 1H), 4.03 (t, *J* = 5.9 Hz, 2H), 3.61 *(d, J* = 17.2 Hz, 1H), 3.38 (d, *J* = 17.4 Hz, 1H), 2.41 - 2.25 (m, 8H), 2.11 - 2.02 (m, 2H).

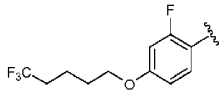
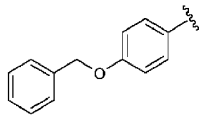
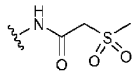
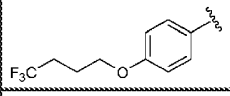
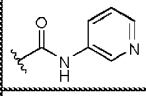
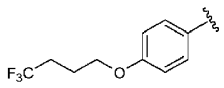
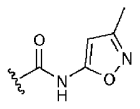
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
251 S-isomer		CF_3	H		R^{13}= $OCHCF_2$	645.4	1H NMR (400 MHz, MeOD) δ 7.52 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.04 - 6.63 (m, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.98 (s, 2H), 3.69 (d, *J* = 16.9 Hz, 1H), 3.45 (d, *J* = 16.9 Hz, 1H), 2.93 (s, 3H), 2.44 - 2.29 (m, 2H), 2.09 - 1.98 (m, 2H).
252 S-isomer		CF_3	H		R^{13} = OCH_3	623.3	1H NMR (400 MHz, MeOD) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H), 6.98 - 6.88 (m, 4H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.99 (s, 2H), 3.79 (s, 3H), 3.66 *(d, J* = 16.9 Hz, 1H), 3.44 *(d, J* = 16.7 Hz, 1H), 2.97 (s, 3H), 2.30 - 2.16 (m, 2H), 1.90 - 1.81 (m, 2H), 1.79 - 1.69 (m, 2H).
253 S-isomer		CF_3	H		R^{13} = CH_3	545.4	1H NMR (400 MHz, MeOD) δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.22 - 7.17 (m, 4H), 7.03 - 6.96 (m, 2H), 4.09 (t, *J* = 6.1 Hz, 2H), 4.02 (q, *J* = 6.8 Hz, 1H), 3.66 *(d, J* = 17.2 Hz, 1H), 3.47 *(d, J* = 16.9 Hz, 1H), 2.46 - 2.32 (m, 5H), 2.10 - 2.00 (m, 2H), 1.19 (d, *J* = 6.8 Hz, 3H).

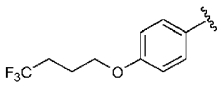
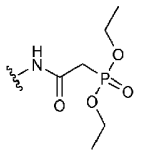
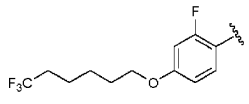
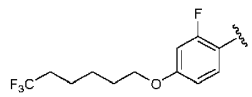
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
254 S-isomer		CF_3	H		R^{13}= $OCHCF_2$	596.2	1H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.39 - 7.33 (m, 2H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.00 - 6.95 (m, 2H), 7.02 - 6.63 (m, 1H), 4.06 (t, *J* = 6.1 Hz, 2H), 3.65 (d, *J*= 16.9 Hz, 1H), 3.42 (d, *J* = 16.7 Hz, 1H), 2.96 (q, *J* = 7.3 Hz, 2H), 2.43 - 2.28 (m, 2H), 2.07 - 1.97 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H).
255 S-isomer		CF_3	H		R^{13} = CH_3	545.3	1H NMR (400 MHz, MeOD) δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.29 - 7.22 (m, 2H), 7.21 - 7.14 (m, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 4.06 (t, *J* = 6.2 Hz, 2H), 3.66 (d, *J* = 16.9 Hz, 1H), 3.45 (d, *J* = 16.7 Hz, 1H), 3.07 (q, *J* = 7.2 Hz, 2H), 2.45 - 2.29 (m, 5H), 2.02 (dd, *J* = 10.2, 5.8 Hz, 2H), 1.06 (t, *J* = 7.2 Hz, 3H).
265 S-isomer		CF_3	H		R^{13} = CH_3	607.1	1H NMR (500 MHz, MeOD) δ 7.88 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.05 - 6.97 (m, 3H), 6.89 (d, *J* = 7.4 Hz, 1H), 6.85 - 6.80 (m, 1H), 4.07 (t, *J* = 6.1 Hz, 2H), 3.68 (s, 3H), 3.63 *(d, J* = 17.3 Hz, 1H), 3.51 *(d, J* = 17.3 Hz, 1H), 2.43 - 2.32 (m, 2H), 2.31 (s, 3 H), 2.07 - 1.98 (m, 2H).

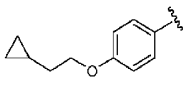
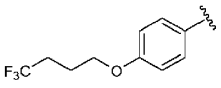
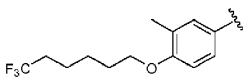
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
266 S-isomer		CF_3	H		$R^{13} = CH_3$	544.1	1H NMR (500 MHz, MeOD) δ 7.50 (dd, *J* = 12.7, 2.5 Hz, 1H), 7.45 - 7.3 (m, 1H), 7.18 *(t, J* = 8.7 Hz, 1H), 7.12 - 7.06 (m, 2H), 6.89 *(d, J*= 8.2 Hz, 2H), 4.16 (t, *J* = 6.1 Hz, 2H), 3.74 (d, J = 17.8 Hz, 1H), 3.68 (d, J = 17.8 Hz, 1H), , 2.52 - 2.32 (m, 2H), 2.29 (s, 3H), 2.13 - 1.98 (m, 2H).
267 S-isomer		CF_3	H		$R^{13} = CH_3$	526.2	
268 S-isomer		CF_3	H		$R^{13} = CH_3$	544.2	1HNMR (500 MHz, DMSO-d_6) δ 9.58 (s, 1H), 7.59 (t, *J* = 9.2 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.99 - 6.92 (m, 2H), 6.89 (d, *J*= 8.1 Hz, 2H), 4.11 (t, *J* = 6.1 Hz, 2H), 3.81 *(d, J* = 17.7 Hz, 1 H), 3.73 *(d, J*= 17.8 Hz, 1H), 2.49 - 2.30 (m, 2H), 2.25 (s, 3H), 2.03-1.78 (m, 2H).
270 R-isomer		CF_3	H		$R^{13} = CH_3$	554.1	1H NMR (400 MHz, MeOD) δ 7.51 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 9.0 Hz, 2H), 6.98 - 6.88 (m, 4H), 4.02 (t, *J* = 6.1 Hz, 2H), 3.99 (s, 2H), 3.79 (s, 3H), 3.66 *(d, J* = 16.9 Hz, 1H), 3.44 (d, *J* = 16.7 Hz, 1H), 2.97 (s, 3H), 2.30 - 2.16 (m, 2H), 1.90 - 1.81 (m, 2H), 1.79 - 1.69 (m, 2H).

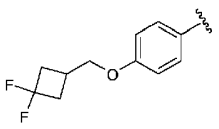
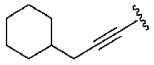
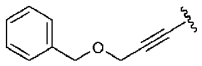
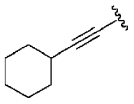
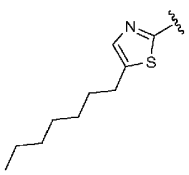
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
271 S-isomer		CF_3	H		R^{13} = CH2CF3	594.1	1H NMR (500 MHz, 1:1 MeOD/$CDCl_3$) δ 7.52 (d, *J*= 8.8 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J*= 8.4, 2.1 Hz, 4H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.73 - 3.64 (m, 1H), 3.60 - 3.49 (m, 1H), 3.35 (d, *J* = 10.7 Hz, 2H), 2.39 - 2.23 (m, 2H), 2.13 - 1.91 (m, 2H).
272 S-isomer		CF_3	H		R^{13} = CH_3	540.3	
273 S-isomer		CF_3	H		R^{13} = CH_3	608.2	1.98 - 2.11 (m, 2H), 2.29 (s, 3H), 2.33 - 2.49 (m, 2H), 3.71 - 3.47 (m, 2H), 3.91 (s, 3H), 4.20 - 4.02 (m, 2H), 6.95 - 7.03 (m, 2H), 7.15 (d, J = 8.3 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 1.4 Hz, 1H), 8.76 (d, J = 1.4 Hz, 1H).
274 S-isomer		CF_3	H		R^{13} = $OCHF_2$	624.1	1H NMR (500 MHz, DMSO-d_6) δ 9.63 (s, 1H), 7.58 (t, *J* = 9.3 Hz, 1H), 7.43 - 6.98 (m, 5H), 6.92 *(d, J*= 12.1 Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.80 (d, *J* = 17.8 Hz, 1H), 3.76 *(d, J* = 17.9 Hz, 1H), 2.37 - 2.14 (m, 2H), 1.83 - 1.66 (m, 2H), 1.63 -1.32 (m, 4H).

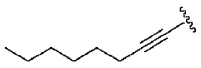
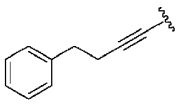
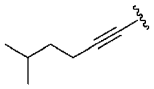
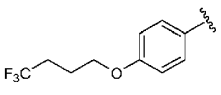
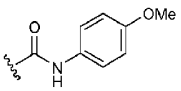
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
275 S-isomer		CF_3	H		R^{13} = $OCHF_2$	630.2	1H NMR (400 MHz, MeOD) δ 8.75 (br. s., 2H), 7.87 (br. s., 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 7.36 *(d, J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.6 Hz, 2H), 7.04 - 6.62 (m, 3H), 4.08 (*t, J* = 5.8 Hz, 2H), 3.75 (br. s., 1H), 3.52 (d, *J* = 16.9 Hz, 1H), 2.45 - 2.29 (m, 2H), 2.09 - 1.99 (m, 2H).
276 S-isomer		CF_3	H		R^{12} R^{13} = 	608.2	1H NMR (500 MHz, MeOD) δ 7.83-7.66 (m, 3H), 7.61 (s, 2H), 7.56 - 7.43 (m, 3H), 7.01 (d, *J*= 8.6 Hz, 1H), 6.85 - 6.67 (m, 2H), 4.05 (d, *J* = 18.0 Hz, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 3.76 (d, *J* = 17.9 Hz, 1H), 2.05-2.20 (m, 2H), 1.91 - 1.72 (m, 2H), 1.74 - 1.45 (m, 4H).
277 S-isomer		CF_3	H		R^{13} = 	567.1	1H NMR (500 MHz, 1:1 $CDCl_3$:MeOD) δ 7.54 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 7.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.07 (t, J = 5.9 Hz, 2H), 3.79 - 3.66 (m, 1H), 3.63 - 3.50 (m, 1H), 2.49 (d, J = 6.9 Hz, 2H), 2.40 - 2.25 (m, 2H), 2.13 - 1.97 (m, 2H), 0.97 - 0.82 (m, 1H), 0.58 - 0.45 (m, 2H), 0.16 (q, J = 5.0 Hz, 2H).

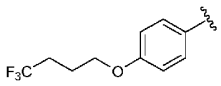
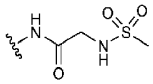
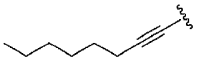
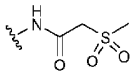
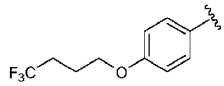
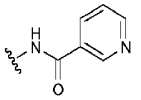
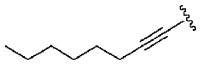
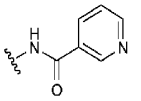
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
278 S-isomer		CF_3	H		$R^{13} = CH_3$	558.2	1H NMR (500 MHz, 1:1 $CDCl_3$:MeOD) δ 7.43 (t, *J* = 9.17 Hz, 1H), 7.02 *(d, J* = 7.93 Hz, 2H), 6.87 (d, *J* = 7.93 Hz, 2H), 6.75 (dd, *J* = 2.48, 8.92 Hz, 1H), 6.71 (dd, *J* = *2.23,* 14.61 Hz, 1H), 3.99 (t, *J* = 5.95 Hz, 2H), 3.87 (d, *J* = 17.83 Hz, 1H), 3.61 *(d, J* = 17.83 Hz, 1H), 2.26 (s, 3H), 2.11-2.21 (m, 2H), 1.80-1.89 (m, 2H), 1.69-1.78 (m, 2H).
279 S-isomer		CF_3	H		$R^{13} = CH_3$	573.2	7.79 (br. s., 1H), 7.46 - 7.38 (m, 7H), 7.22 - 7.17 (m, 2H), 7.15 - 7.10 (m, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.69 (br. s., 1H), 5.07 (s, 2H), 3.82 (br. s., 2H), 3.63 *(d, J* = 17.2 Hz, 1H), 3.37 (d, *J* = 17.2 Hz, 1H), 2.95 (s, 3H), 2.36 (s, 3H).
280 S-isomer		CF_3	H		$R^{13} = OCHF_2$	630.2	
281 S-isomer		CF_3	H		$R^{13} = CH_3$	582.2	1H NMR (500MHz, MeOD) δ 7.56 (d, J = 8.92 Hz, 2H), 7.30 (d, J = 8.42 Hz, 2H), 7.10 (d, J = 7.93 Hz, 2H), 6.97 (d, J = 8.92 Hz, 2H), 6.37 (s, 1H), 4.06 (m, 2H), 3.59 (d, J = 17.83 Hz, 1H), 3.43 (d, J = 17.34 Hz, 1H), 2.32 (m, 2H), 2.30 (s, 3H), 2.22 (s, 3H), 2.06 (m, 2H).

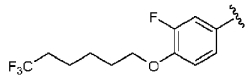
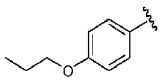
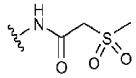
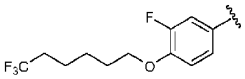
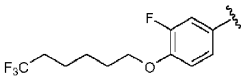
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
282 S-isomer		CF_3	H		$R^{13} = CH_3$	651.2	1H NMR (500MHz, MeOD) δ 7.61 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 5.9 Hz, 4H), 6.93 (d, *J* = 8.9 Hz, 2H), 4.33 (br. s., 1H), 4.07 - 4.02 (m, 2H), 4.02 - 3.94 (m, 4H), 3.67 - 3.56 (m, 1H), 3.37 - 3.34 (m, 1H), 2.94 - 2.78 (m, 2H), 2.33 (s, 5H), 2.09 - 2.00 (m, 2H), 1.22 (d, *J* = 1.5 Hz, 6H).
283 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	602.2	1H NMR (500 MHz, DMSO-d_6) δ 9.39 (s, 1H), 7.56 (t, *J* = 9.3 Hz, 1H), 6.92 *(t, J* = 8.6 Hz, 4H), 6.81 (d, *J*= 8.8 Hz, 2H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.99 (q, *J*= 6.9 Hz , 2H), 3.82 *(d, J*= 17.3 Hz, 1H), 3.69 *(d, J*= 17.7 Hz, 1H), 2.34 - 2.15 (m, 2H), 1.85 - 1.70 (m, 2H), 1.65 - 1.42 (m, 4H), 1.29 (t, *J= 6.9* Hz, 3H).
284 S-isomer		CF_3	H		$R^{13} = CH_2CF_3$	640.1	1H NMR (500 MHz, DMSO-d_6) δ 9.36 (w, 1H), 7.59 (t, *J* = 9.3 Hz, 1H), 7.20 *(d, J* = 7.9 Hz, 2H), 7.07 - 6.74 (m, 4H), 4.03 (t, *J* = 6.4 Hz, 2H), 3.76 *(d, J*= 17.4 Hz, 1H), 3.70 *(d, J*= 17.7 Hz, 1H), 3.58 (dd, *J* = 23.3, 11.7 Hz, 2H), 2.33 - 2.16 (m, 2H), 1.86 - 1.68 (m, 2H), 1.545-1.60 (m, 4H).

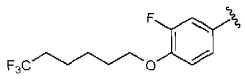
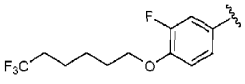
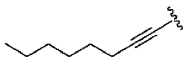
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
285 S-isomer		CF_3	H		$R^{13} = CH_3$	484.1	1H NMR (500 MHz, DMSO-d_6) δ 9.58 - 9.48 (m, 1H), 7.65 - 7.55 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.04 - 6.97 (m, 2H), 6.94 - 6.85 (m, 2H), 4.06 (s, 2H), 3.69 (s, 2H), 2.24 (s, 3H), 1.63 (q, *J* = 6.6 Hz, 2H), 1.35 - 1.08 (m, 1H), 0.94 - 0.77 (m, 1H), 0.51 - 0.38 (m, 2H), 0.16 - 0.06 (m, 2H)
286 S-isomer		CF_3	H		R^{11} = F R^{13} = CH_3	544.2	1H NMR (500 MHz, DMSO-d_6) δ 7.62 (d, J = 8.80 Hz, 2H), 7.02 (d, J = 8.80 Hz, 2H), 7.01 (m, 1H), 6.98 (t, J = 7.98 Hz, 1H), 6.93 (d, J = 11.55 Hz, 1H), 4.08 (t, J = 6.93 Hz, 2H), 3.68 (d, J = 18.16 Hz, 1H), 3.62 (d, J = 17.88 Hz, 1H), 2.42 (m, 2H), 2.28 (s, 3H), 1.95 (m, 2H).
287 S-isomer		CF_3	H		$R^{13} = CH_3$	568.2	1H NMR (500 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.49 (s, 1H), 7.45 (*d*, *J*= 8.80 Hz, 1H), 7.07 (d, *J* = 7.98 Hz, 2H), 6.98 (d, J = 8.80 Hz, 1H), 6.89 *(d, J*= 8.25 Hz, 2H), 4.00 (t, J = 6.19 Hz, 2H), 3.66 (s, 2H), 2.24 (s, 3H), 2.20-2.32 (m, 2H), 2.17 (s, 3H), 1.71-1.80 (m, 2H), 1.47-1.61 (m, 4H).

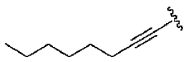
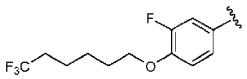
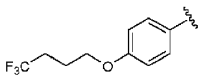
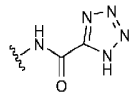
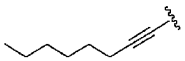
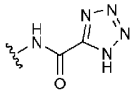
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
288 S-isomer		CF_3	H		$R^{13} = CH_3$	520.0	1H NMR (500 MHz, DMSO-d_6) δ 9.67 (s, 1H), 8.15 (d, J = 4.1 Hz, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 4.1 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 4.03 (t, J = 6.2 Hz, 2H), 3.98 (d, J = 17.6 Hz, 1H), 3.62 (d, J = 17.3 Hz, 1H), 2.45 - 2.33 (m, 2H), 2.31 - 2.23 (m, 1H), 1.94 - 1.79 (m, 2H), 1.23 - 1.11 (m, 2H), 0.87 - 0.77 (m, 2H).
289 S-isomer		CF_3	H		$R^{13}=CH_3$	444.1	7.17 (d, *J* = 7.9 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.84 (s, 1H), 3.39 (AB quartet, *J* = 18.7 Hz, 2H), 2.36 (s, 3H), 2.13 (d, *J* = 6.6 Hz, 2H), 1.77 - 1.60 (m, 5H), 1.55 - 1.42 (m, 1H), 1.29 - 0.88 (m, 5H).
290 S-isomer		CF_3	H		$R^{13} = CH_3$	468.1	7.36 - 7.27 (m, 5H), 7.18 (s, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 7.01 *(d, J* = 8.1 Hz, 2H), 4.57 (AB quartet, *J* = 11.7 Hz, 2H), 4.22 (s, 2H), 3.39 (AB quartet, *J* = 18.9 Hz, 2H), 2.34 (s, 3H).
291 S-isomer		CF_3	H		$R^{13} = CH_3$	430.1	7.19 (d, *J* = 7.9 Hz, 2H), 7.06 *(d, J* = 8.1 Hz, 2H), 6.59 (s, 1H), 3.38 (AB quartet, *J* = 18.9 Hz, 2H), 2.49 - 2.41 (m, 1H), 2.38 (s, 3H), 1.81 - 1.72 (m, 2H), 1.65 (dd, *J* = 5.9, 2.4 Hz, 2H), 1.54 - 1.40 (m, *J* = 12.5, 8.9, 8.9, 8.9 Hz, 3H), 1.38 - 1.28 (m, 3H).
292 Rac		CF_3	H		$R^{13}=CH_3$	394.5	

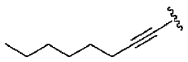
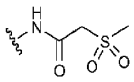
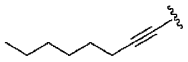
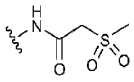
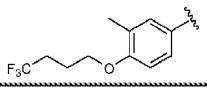
Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
293 S-isomer		CF_3	H		$R^{13} = CH_3$	432.1	7.19 (d, *J* = 7.9 Hz, 2H), 7.06 *(d, J* = 8.1 Hz, 2H), 6.67 (s, 1H), 3.38 (AB quartet, *J* = 18.9 Hz, 2H), 2.37 (s, 3H), 2.23 *(t, J* = 7.0 Hz, 2H), 1.51 (quin, *J* = 7.3 Hz, 2H), 1.40 - 1.22 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H).
294 S-isomer		CF_3	H		$R^{13} = OCH_3$	468.1	1H NMR (500 MHz, MeOD) δ 7.31 - 7.15 (m, 5H), 6.96 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 3.79 (s, 3H), 3.34 (AB quartet, J = 18.3 Hz, 2H, partially overlapping with solvent), 2.85 (t, J = 7.2 Hz, 2H), 2.58 (t, J = 7.4 Hz, 2H).
295 S-isomer		CF_3	H		R^{13} = OCH;	434.1	1H NMR (500 MHz, MeOD) δ 7.01 (d, J = 8.9 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 3.77 (s, 3H), 3.40 (s, 2H), 2.29 (t, J = 7.4 Hz, 2H), 1.69 (dt, J = 13.5, 6.9 Hz, 1H), 1.45 (q, J = 7.4 Hz, 2H), 0.91 (dd, J = 6.9, 2.0 Hz, 6H).
296 S-isomer		CF_3	H		R^{11} = F R^{13} = CH_3	625.2	1H NMR (500 MHz, DMSO-d_6) δ 7.55 (d, J = 8.80 Hz, 2H), 7.31 (d, J = 9.08 Hz, 2H), 7.13 (m, 1H), 7.06 (d, J = 11.83 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 7.70 Hz, 1H), 6.80 (d, J = 9.08 Hz, 2H), 4.08 (m, 2H), 3.70 (m, 2H), 3.68 (s, 3H), 2.43 (m, 2H), 2.27 (s, 3H), 1.95 (m, 2H).

Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
297 S-isomer		CF_3	H		$R^{13} = CH_3$	608.1	7.43 *(d, J* = 8.6 Hz, 2H), 7.20 - 7.16 (m, 2H), 7.15 - 7.10 (m, 2H), 6.93 *(d, J* = 8.8 Hz, 2H), 6.57 (s, 1H), 5.10 (br. s., 1H), 4.03 *(t, J* = 5.9 Hz, 2H), 3.72 (br. s., 2H), 3.62 *(d, J* = 17.6 Hz, 1H), 3.38 (*d, J* = 17.8 Hz, 1 H), 2.80 - 2.74 (m, 3H), 2.40 - 2.24 (m, 5H), 2.12 - 2.02 (m, 2H)
298 S-isomer		CF_3	H		$R^{13} = CH_3$	499.1	7.74 (br. s., 1H), 7.26 - 7.20 (m, 4H), 5.88 (s, 1H), 3.84 (s, 2H), 3.29 (ABq, *J* = 17.6 Hz, 2H), 2.95 (s, 3H), 2.37 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.57 - 1.48 (m, 2H), 1.41 - 1.25 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H)
299 S-isomer		CF_3	H		$R^{13} = CH_3$	578.1	9.08 (br. s., 1H), 8.77 (d, *J* = 4.2 Hz, 1H), 8.37 (br. s., 1H), 8.25 (br. s., 1H), 7.65 (br. s., 1H), 7.46 *(d, J* = 8.8 Hz, 2H), 7.19 - 7.11 (m, 4H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.88 (s, 1H), 4.04 (t, *J* = 5.9 Hz, 2H), 3.66 *(d, J* = 17.6 Hz, 1H), 3.43 *(d, J* = 17.4 Hz, 1H), 2.40 - 2.25 (m, 5H), 2.12 - 2.03 (m, 2H).
300 S-isomer		CF_3	H		$R^{13} = CH_3$	484.2	1H NMR (400 MHz, MeOD) δ 9.00 (br. s., 1H), 8.79 (dd, *J* = 5.3, 1.3 Hz, 1H), 8.46 (d, *J* = 7.3 Hz, 1H), 7.78 (dd, *J* = 8.0, 5.4 Hz, 1H), 7.33 *(d, J* = 8.1 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 3.38 (s, 2H), 2.35 - 2.27 (m, 5H), 1.60 - 1.50 (m, 2H), 1.48 - 1.38 (m, 2H), 1.35 - 1.27 (m, 4H), 0.93 - 0.87 (m, 3H).

Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
301 S-isomer		CF_3	H		R^{13} = $OCHF_2$	624.2	1H NMR (500 MHz, DMSO-d_6) δ 9.53 (s, 1H), 7.65 (dd, *J* = 13.0, 2.0 Hz, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.46 - 6.88 (m, 6H), 4.11 (t, *J* = 6.3 Hz, 2H), 3.77 *(d, J* = 17.9 Hz, 1H), 3.72 *(d, J* = 17.9 Hz, 1H), 2.36 - 2.08 (m, 2H), 1.88 - 1.71 (m, 2H), 1.67 - 1.34 (m, 4H).
302 S-isomer		CF_3	H		R^{13} = CH_3	525.0	1HNMR (400 MHz, MeOD) δ 7.50 (d, *J* = 8.8 Hz, 2H), 7.23 - 7.15 (m, 4H), 6.93 (d, *J* = 9.0 Hz, 2H), 4.00 - 3.92 (m, 4H), 3.66 (d, *J* = 17.2 Hz, 1H), 3.43 *(d, J* = 16.9 Hz, 1H), 2.93 (s, 3H), 2.32 (s, 3H), 1.79 (sxt, *J* = 7.0 Hz, 2H), 1.04 (t, *J* = 7.4 Hz, 3H).
303 S-isomer		CF_3	H		R^{13} = CH_3	572.3	
304 S-isomer		CF_3	H		R^{12} R^{13} = 	608.3	1HNMR (500 MHz, DMSO-d_6) δ 9.57 (br. s., 1H), 7.84 (dd, *J* = 7.84, 13.34 Hz, 2H), 7.71-7.77 (m, 2H), 7.67 *(d, J* = 12.93 Hz, 1H), 7.47-7.57 (m, 3H), 7.26 *(t, J* = 8.94 Hz, 1H), 6.93 (d, *J* = 8.80 Hz, 1H), 5.56 (d, *J* = 7.70 Hz, 1H), 4.10 (t, *J* = 6.19 Hz, 2H), 3.79-3.92 (m, 2H), 2.20-2.33 (m, 2H), 1.68-1.83 (m, 2H), 1.45-1.65 (m, 4H).

Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
305 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	602.3	1HNMR (500 MHz, DMSO-d_6) δ 9.38-9.54 (m, 1H), 7.63 (d, *J* = 13.20 Hz, 1H), 7.46 (d, *J*= 8.80 Hz, 1H), 7.24 (t, *J* = 8.80 Hz, 1H), 6.96 *(d, J* = 8.53 Hz, 2H), 6.79 (d, *J* = 8.53 Hz, 2H), 4.09 (t, *J* = 6.33 Hz, 2H), 3.98 (q, *J* = 6.88 Hz, 2H), 2.20-2.34 (m, 2H), 1.77 (quin, *J* = 6.81 Hz, 2H), 1.46-1.61 (m, 4H), 1.28 (t, *J* = 7.02 Hz, 3H).
306 S-isomer		CF_3	H		R^{13} = CH_2CF_3	640.2	1HNMR (500 MHz, DMSO-d_6) δ 9.56 (br. s., 1H), 7.65 *(d, J* = 12.93 Hz, 1H), 7.49 (d, *J* = 8.80 Hz, 1H), 7.20-7.28 (m, 3H), 7.03 *(d, J* = 7.98 Hz, 2H), 4.10 (t, *J* = 6.33 Hz, 2H), 3.71-3.81 (m, 2H), 3.61 (q, *J* = 11.55 Hz, 2H), 2.20-2.33 (m, 2H), 1.78 (quin, *J* = 6.74 Hz, 2H), 1.44-1.61 (m, 4H)
307 S-isomer		CF_3	H		R^{13} = $OCHF_2$	484.1	7.19 *(d, J* = 8.8 Hz, 2H), 7.12 *(d, J* = 8.6 Hz, 2H), 6.78 (br. s., 1H), 6.56 (t, *J* = 73.1 Hz, 1H), 3.37 (AB quartet, *J* = 18.9 Hz, 2H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.52 (quin, *J* = 7.3 Hz, 2H), 1.41 - 1.21 (m, 6H), 0.87 (t, *J* = 6.8 Hz, 3H).

Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
308 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	462.1	7.10 (d, *J* = 9.0 Hz, 2H), 6.85 *(d, J* = 8.8 Hz, 2H), 6.72 (s, 1H), 4.04 (q, *J*= 7.0 Hz, 2H), 3.37 (AB quartet, *J* = 18.9 Hz, 2H), 2.22 *(t, J* = 7.2 Hz, 2H), 1.51 (quin, *J* = 7.3 Hz, 2H), 1.42 (t, *J* = 7.0 Hz, 3H), 1.39 - 1.22 (m, 6H), 0.87 (t, *J* = 6.6 Hz, 3H).
309 S-isomer		CF_3	H		R^{12} R^{13} = 	612.1	1HNMR (500 MHz, DMSO-d_6) δ 9.52 (br. s., 1H), 7.63 (d, *J* = 13.20 Hz, 1H), 7.46 (d, *J* = 8.53 Hz, 1H), 7.25 (t, *J* = 8.94 Hz, 1H), 6.88 *(d, J* = 7.98 Hz, 1H), 6.83 (s, 1H), 6.58 (d, *J* = 7.98 Hz, 1H), 4.09 (t, *J* = 6.19 Hz, 2H), 3.64-3.75 (m, 2H), 2.54-2.67 (m, 4H), 2.20-2.34 (m, 2H), 1.77 (quin, *J* = 6.74 Hz, 2H), 1.67 (br. s., 4H), 1.44-1.61 (m, 4H).
310 S-isomer		CF_3	H		R^{13} = CH_3	569.0	1HNMR (400 MHz, MeOD) δ 7.56 (d, *J* = 8.8 Hz, 2H), 7.26 - 7.21 (m, 2H), 7.18 - 7.12 (m, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 4.07 (t, *J* = 6.2 Hz, 2H), 3.73 *(d, J* = 17.2 Hz, 1H), 3.51 *(d, J* = 16.9 Hz, 1H), 2.43 - 2.32 (m, 2H), 2.29 (s, 3H), 2.08 - 1.98 (m, 2H).
311 S-isomer		CF_3	H		R^{13} = CH_3	475.1	1HNMR (400 MHz, MeOD) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 7.9 Hz, 2H), 3.37 (s, 2H), 2.34 - 2.26 (m, 5H), 1.53 (d, *J* = 7.3 Hz, 2H), 1.42 (br. s., 2H), 1.34 -1.25 (m, 4H), 0.92 - 0.86 (m, 3H).

Example	R1	R2	R3 = R4	R6	R11-R15	[M+H]	1HNMR (400 MHz, $CDCl_3$)
312 S-isomer		CF_3	H		R^{13} = OCH_2CH_3	529.4	7.73 (br. s., 1H), 7.31 *(d, J*= 8.6 Hz, 2H), 6.92 *(d, J* = 8.8 Hz, 2H), 5.91 (s, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.86 (s, 2H), 3.30, 3.28 (ABq, *J* = 18.3 Hz, 2H), 2.99 (s, 3H), 2.23 (t, *J* = 7.0 Hz, 2H), 1.52 (quin, *J* = 7.3 Hz, 2H), 1.43 (t, *J* = 6.9 Hz, 3H), 1.41 - 1.22 (m, 7H), 0.89 (t, *J* = 6.9 Hz, 2H).
313 S-isomer		CF_3	H		R^{13} = $OCHF_2$	551.0	7.85 (br. s., 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.55 (t, *J* = 72.4 Hz, 1H), 5.97 (s, 1H), 3.84 (s, 2H), 3.30, 3.28 (ABq, *J* = 17.8 Hz, 2H), 2.89 (s, 3H), 2.24 (t, *J* = 7.0 Hz, 2H), 1.52 (dt, *J* = 14.6, 7.2 Hz, 2H), 1.43 - 1.23 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H).
314 S-isomer		CF_3	H		R^{13} = CH_3	540.3	

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- WO2010095767A [0004]
- US2010093771A [0005]
- US5614492A [0238]

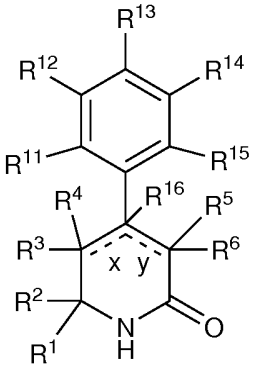
Non-patent literature cited in the description

- **YEN, C.L. et al.**Nat. Med., 2009, vol. 15, 4442-446 [0003] [0003] [0210] [0210]
- Hawley's Condensed Chemical DictionaryJ. Wiley & Sons, Inc.20070000 [0167]
- **WUTS, P. G. M.GREENE, T.W.**Projecting Groups in Organic SynthesisWiley20070000 [0181]
- The Peptides: Analysis, Synthesis, BiologyAcademic Press19810000vol. 3, [0181]
- **REMINGTON**The Science and Practice of PharmacyPharmaceutical Press20120000 [0189]
- **WUTS, P. G. M.GREENE, T.W.**Protecting Groups in Organic SynthesisWiley20070000 [0195]
- Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic ChemistryPergamon Press19910000 [0195]
- **SMITH, M. B.MARCH, J.**March's Advanced Organic Chemistry: Reactions, Mechanism, and StructureWiley & Sons20070000 [0195]
- Comprehensive Organic Functional Groups Transformations IIElsevier Science Inc.20040000 [0195]
- **LAROCK, R.C.**Comprehensive Organic TransformationsVCH Publishers, Inc.19990000 [0195]
- **T. P. TANGJ. A ELLMAN**J. Org. Chem., 1999, vol. 64, 12-13 [0206] [0207]
- J. Org. Chem., 2002, vol. 67, 7819-7832 [0206] [0207]
- **OKAWA, M. et al.**Biochem. Biophys. Res. Commun., 2009, vol. 390, 3377-381 [0210]
- **SEETHALA et al.**Anal. Biochem., 2008, vol. 383, 2144-150 [0218]
- **FORD et al.**J. Am. Med. Assoc., 2002, vol. 287, 356-359 [0223]
- **ARBEENY et al.**Curr. Med. Chem. - Imm., Endoc. & Metab. Agents, 2001, vol. 1, 1-24 [0223]
- **ALLEN, L. V. JR. et al.**Rernaington: The Science and Practice of PharmacyPharmaceutical Press20120000vol. 2, [0226]
- **FYFE, M.C.T. et al.**Drugs of the Future, 2009, vol. 34, 8641-653 [0236]
- **MOHLER, M.L. et al.**Medicinal Research Reviews, 2009, vol. 29, 1125-195 [0236]
- **MIZUNO, C.S. et al.**Current Medicinal Chemistry, 2008, vol. 15, 61-74 [0236]
- **MELNIKOVA, I. et al.**Nature Reviews Drug Discovery, 2006, vol. 5, 369-370 [0238]
- **JONES, D.**Nature Reviews: Drug Discovery, 2009, vol. 8, 833-834 [0238]
- **OBICI, S.**Endocrinology, 2009, vol. 150, 62512-2517 [0238]
- **ELANGBAM, C.S.**Vet. Pathol., 2009, vol. 46, 110-24 [0238]

ARYLDIHYDROPYRIDONER OG PIPERIDONER SOM MGA2-INHIBITORER

PATENTKRAV

1. Forbindelse med formlen (I):



(I)

eller en stereoisomer, en tautomer, et farmaceutisk acceptabelt salt eller et solvat deraf, hvor:

$\overline{\text{---}}$ betegner en enkelt eller dobbelt binding;

x og y begge både kan være en enkelt binding; når x er en dobbelt binding, så er y en enkelt binding, og R^4 og R^{16} er fraværende; når y er en dobbelt binding, så er x en enkelt binding, og R^5 og R^{16} er fraværende;

R^1 uafhængigt er udvalgt fra gruppen bestående af: -CONH(C_{4-18}-alkyl), -CONHC_{2-8}-haloalkyl, -CONH$(CH_2)_{1-8}$-Ph, -CONHCH_2COC_{2-8}-alkyl, -$(CH_2)_m$-(C_{3-10}-carbocyklus substitueret med 0-2 R^b og 0-2 R^g), -$(CH_2)_m$-(5- til 6-leddet heteroaryl der omfatter: carbonatomer og 1-4 heteroatomer, der er udvalgt fra N, NR^e, O og S; hvor heteroarylen er substitueret med 0-1 R^b og 0-2 R^g), og en C_{1-12}-hydrocarbonkæde, der er substitueret med 0-3 R^a; hvor hydrocarbonkæden kan være lige eller forgrenet, mættet eller umættet;

R^2 uafhængigt er udvalgt fra gruppen bestående af: C_{1-4}-alkyl, C_{3-4}-cycloalkyl og C_{1-4}-haloalkyl;

R^3 uafhængigt er udvalgt fra gruppen bestående af: H, F, Cl, C_{1-4}-alkyl og CN;

R^4 og R^5 uafhængigt er udvalgt fra gruppen bestående af: H, F, Cl, og C_{1-4}-alkyl;

når x er en enkelt binding, kan R^3 og R^4 være kombineret med det carbonatom, hvortil de er bundet, for at danne en 3- til 6-leddet carbocyklus;

R^6 uafhængigt er udvalgt fra gruppen bestående af: H, halo, C_{1-4}-alkyl, NO_2, R^c, -$(CH_2)_n$-$(X)_t$-$(CH_2)_m R^c$, NH_2, -CONH(C_{1-6}-alkyl), -NHCO$X_1SO_2R^j$, -NHCO$CH_2PO(OEt)_2$, -NHCOCOR^j, -NHCOCH(OH)R^j, -NHCOCH_2COR^j, -NHCONHR^j og -OCONR^fR^j;

X uafhængigt er udvalgt fra gruppen bestående af: O, S, NH, CONH og NHCO;

X_1 uafhængigt er C_{1-4}-hydrocarbonkæde eventuelt substitueret med C_{1-4}-alkyl eller C_{3-4}-cycloalkyl;

når y er en enkelt binding, kan R^5 og R^6 kombineres med det carbonatom, hvortil de er bundet, for at danne en 3- til 6-leddet carbocyklus;

R^{11}, R^{12}, R^{13}, R^{14} og R^{15} uafhængigt er udvalgt fra gruppen bestående af: H, halo, C_{1-4}-alkyl substitueret med 0-2 R^i, C_{1-4}-alkoxy, C_{1-4}-haloalkyl, C_{1-4}-haloalkoxy, -$(CH_2)_m$-C_{3-6}-cycloalkyl, CN, NR^fR^j,

OR^j, SR^j, $NHCO_2(C_{1-4}$-alkyl), $NHSO_2(C_{1-4}$-alkyl), og en 4- til 6-leddet heterocyklus, der omfatter: carbonatomer og 1-4 heteroatomer, der er udvalgt fra N, NR^e, O og S;

alternativt kombineres R^{11} og R^{12}, sammen med de carbonatomer, hvortil de er bundet, for at danne en 5- til 6-leddet carbocyklisk ring eller en 5- til 6-leddet heterocyklisk ring, der omfatter: carbonatomer og 1-3 heteroatomer, der er udvalgt fra N, NR^e, O og S;

alternativt kombineres R^{12} og R^{13}, sammen med de carbonatomer, hvortil de er bundet, for at danne en 5- til 6-leddet carbocyklisk ring eller en 5- til 6-leddet heterocyklisk ring, der omfatter: carbonatomer og 1-3 heteroatomer, der er udvalgt fra N, NR^e, O og S;

R^{16} uafhængigt er udvalgt fra gruppen bestående af: H og C_{1-4}-alkyl;

R^a er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: halo, OH, C_{1-6}-alkoxy, C_{1-6}-haloalkyl, C_{1-6}-haloalkoxy, $N(C_{1-4}\text{-alkyl})_2$, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$ og $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^b er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: halo, OH, C_{1-10}-alkyl, C_{1-10}-alkoxy, C_{1-10}-haloalkyl, C_{1-10}-haloalkoxy, C_{1-10}-alkylthio, C_{1-10}-haloalkylthio, $N(C_{1-4}\text{-alkyl})_2$, $-CONH(CH_2)_{4-20}H$, $-O(CH_2)_sO(C_{1-6}\text{-alkyl})$, R^c, $-(CH_2)_n-(X)_t-(CH_2)_mR^c$ og $-(CH_2)_n-(CH_2O)_m-(CH_2)_nR^f$;

R^c er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: C_{3-6}-cycloalkyl substitueret med 0-2 R^d, C_{3-6}-cycloalkenyl substitueret med 0-2 R^d, $-(CH_2)_m-$(phenyl substitueret med 0-3 R^d), og en 5- til 6-leddet heterocyklus, der omfatter: carbonatomer og 1-4 heteroatomer, der er udvalgt fra N, NR^e, O, og S; hvor heterocyklussen er substitueret med 0-2 R^d;

R^d er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: halo, OH, CN, NO_2, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-haloalkyl, C_{1-4}-haloalkoxy, tetrazolyl, OBn og phenyl substitueret med 0-2 R^h;

R^e er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: H, C_{1-8}-alkyl, C_{1-8}-haloalkyl, benzyl eventuelt substitueret med C_{1-4}-alkoxy, $CO(C_{1-4}$-alkyl) og COBn;

R^f er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: H og C_{1-4}-alkyl;

R^g, R^h og R^i er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: halo, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-haloalkyl, og C_{1-4}-haloalkoxy;

R^j er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: C_{1-4}-alkyl, C_{3-4}-cycloalkyl og phenyl;

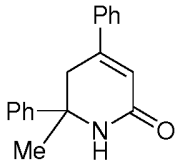
n, ved hver forekomst, uafhængigt er 0 eller 1;

m, ved hver forekomst, uafhængigt er 0, 1, 2, 3 eller 4;

s, ved hver forekomst, uafhængigt er 1, 2 eller 3; og

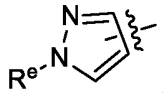
t, ved hver forekomst, uafhængigt er 0 eller 1;

under forudsætning af at den følgende forbindelse er udelukket:



2. Forbindelse ifølge krav 1, hvor:

R^1 uafhængigt er udvalgt fra gruppen bestående af: -$CONHC_{4-18}$-alkyl, -$CONH(CH_2)_{1-8}$ Ph, C_{1-12}-alkyl substitueret med 0-2 R^a, C_{1-12}-alkenyl substitueret med 0-2 R^a, C_{1-12}-alkynyl substitueret med 0-2 R^a, -$(CH_2)_m$-(phenyl substitueret med 0-1 R^b og 0-2 R^g), -$(CH_2)_m$-(C_{3-6}-cycloalkyl substitueret med 0-1 R^b), og -$(CH_2)_m$-(5- til 6-leddet heteroaryl substitueret med 0-1 R^b og 0-2 R^g), hvor heteroarylen er udvalgt fra: pyridyl, oxazolyl, thiazolyl og



.

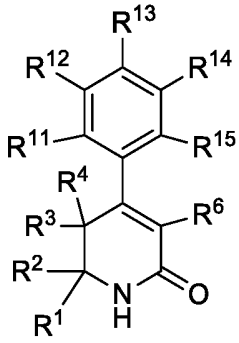
3. Forbindelse ifølge krav 1 eller krav 2, hvor:

R^{11} og R^{15} uafhængigt er udvalgt fra gruppen bestående af: H, C_{1-4}-alkyl og halo;

R^{12} og R^{14} uafhængigt er udvalgt fra gruppen bestående af: H, halo, C_{1-4}-alkyl og C_{1-4}-alkoxy; og

R^{13} uafhængigt er udvalgt fra gruppen bestående af: H, halo, C_{1-4}-alkyl substitueret med 0-1 R^i, C_{1-4}-alkoxy, C_{1-4}-haloalkyl, C_{1-4}-haloalkoxy, -$(CH_2)_m$-C_{3-4} cycloalkyl, CN, NR^fR^j, SR^j, $NHCO_2$(C_{1-4}-alkyl), $NHSO_2$(C_{1-4}-alkyl), og en 4- til 6-leddet heterocyklus, der omfatter: carbonatomer og 1-4 heteroatomer, der er udvalgt fra N, NR^e, O og S.

4. Forbindelse ifølge et hvilket som helst af kravene 1 til 3, hvor forbindelsen er med formlen (II):

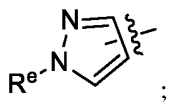


(II)

eller en stereoisomer, en tautomer, et farmaceutisk acceptabelt salt eller et solvat deraf.

5. Forbindelse ifølge et hvilket som helst af kravene 1 til 4, hvor:

R^1 uafhængigt er udvalgt fra gruppen bestående af: C_{1-6}-alkyl, C_{3-6}-cycloalkyl, -$CONHC_{4-18}$-alkyl, -$CONHC_{2-8}$-haloalkyl, -$CONH(CH_2)_{1-8}$ Ph, -$(CH_2)_m$-(phenyl substitueret med 1 R^b og 0-2 R^g), og en 5- til 6-leddet heteroaryl substitueret med 0-1 R^b og 0-2 R^g, hvor heteroarylen er udvalgt fra: pyridyl, oxazolyl, thiazolyl og



;

R^2 uafhængigt er udvalgt fra gruppen bestående af: C_{1-4}-alkyl og C_{1-4}-haloalkyl;

R^3 uafhængigt er udvalgt fra gruppen bestående af: H og F;

R^4 uafhængigt er udvalgt fra gruppen bestående af: H og F;

R^6 uafhængigt er udvalgt fra gruppen bestående af: NH_2, -CONH(C_{1-6}-alkyl), R^c, -$(CH_2)_n$-$(X)_t$-$(CH_2)_m R^c$, -NHCO$(CH_2)SO_2$(C_{1-4}-alkyl), -NHCOCH_2PO$(OEt)_2$, -NHCOCO(C_{1-4}-alkyl), -NHCOCH(OH)(C_{1-4}-alkyl), -NHCOCH_2CO(C_{1-4}-alkyl), -NHCONH(C_{1-4}-alkyl) og -OCONH(C_{1-4}-alkyl);

R^{11} og R^{15} uafhængigt er udvalgt fra gruppen bestående af: H, C_{1-4}-alkyl og halo;

R^{12} og R^{14} uafhængigt er udvalgt fra gruppen bestående af: H, halo, C_{1-4}-alkyl og C_{1-4}-alkoxy;

R^{13} uafhængigt er udvalgt fra gruppen bestående af: H, halo, C_{1-4}-alkyl substitueret med 0-1 C_{1-4}-alkoxy, C_{1-4}-alkoxy, C_{1-4}-haloalkyl, C_{1-4}-haloalkoxy, -$(CH_2)_m$-C_{3-4}-cycloalkyl, CN, N(C_{1-4}-alkyl)$_2$, NHCO$_2$(C_{1-4}-alkyl), NHSO$_2$(C_{1-4}-alkyl), pyrazolyl og morpholinyl;

alternativt kombineres R^{12} og R^{13}, sammen med de carbonatomer, hvortil de er bundet, for at danne en 5- til 6-leddet carbocyklisk ring eller en 5- til 6-leddet heterocyklisk ring, der omfatter: carbonatomer og 1-3 heteroatomer, der er udvalgt fra N, NR^e, O og S;

R^b er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: halo, OH, C_{1-8}-alkyl, C_{1-8}-alkoxy, C_{1-8}-haloalkyl, C_{1-10}-haloalkoxy, -O$(CH_2)_s$O(C_{1-6}-alkyl), N(C_{1-4}-alkyl)$_2$, -CONH$(CH_2)_{6-20}$H, -$(CH_2)_m$(C_{3-6}-cycloalkyl), -$(CH_2)_m$(C_{4-6}-cycloalkenyl), -O$(CH_2)_m$(C_{3-6}-cycloalkyl), 4-C_{1-4}-alkoxy-Ph, -O$(CH_2)_m$Ph, morpholinyl, pyridyl, 2-C_{1-4}-alkoxy-pyridin-5-yl, pyrimidinyl, pyrazinyl og -O-pyrimidinyl;

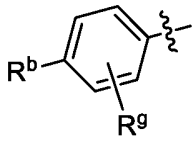
R^g er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: halo, C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-haloalkyl og C_{1-4}-haloalkoxy;

m, ved hver forekomst, uafhængigt er 0, 1, 2 eller 3; og

s, ved hver forekomst, uafhængigt er 1, 2 eller 3.

6. Forbindelse ifølge et hvilket som helst af kravene 1 til 5, hvor:

R^1 uafhængigt er udvalgt fra gruppen bestående af: C_{1-6}-alkyl, -CONHC_{4-18} alkyl, -CONH$(CH_2)_{1-8}$Ph, og



;

R^6 uafhængigt er udvalgt fra gruppen bestående af: NH_2, -CONH(C_{1-6}-alkyl), -NHCOCH_2PO$(OEt)_2$, -NHCO$(CH_2)SO_2$(C_{1-4}-alkyl), R^c, OR^c, -CONHR^c, og -NHCOR^c;

R^{12} uafhængigt er udvalgt fra gruppen bestående af: H, halo, C_{1-4}-alkyl og C_{1-4}-alkoxy;

R^{13} uafhængigt er udvalgt fra gruppen bestående af: H, halo, C_{1-4}-alkyl substitueret med 0-1 C_{1-4}-alkoxy, C_{1-4}-alkoxy, C_{1-4}-haloalkyl, C_{1-4}-haloalkoxy, -$(CH_2)_m$-C_{3-4}-cycloalkyl, CN, N(C_{1-4}-alkyl)$_2$, NHCO$_2$(C_{1-4}-alkyl), NHSO$_2$(C_{1-4}-alkyl), pyrazolyl og morpholinyl;

alternativt kombineres R^{12} og R^{13}, sammen med de carbonatomer, hvortil de er bundet, for at danne en 5- til 6-leddet carbocyklisk ring eller en 5- til 6-leddet mættet heterocyklisk ring, der omfatter: carbonatomer og 1-2 oxygenatomer;

R^{14} uafhængigt er udvalgt fra gruppen bestående af: H og C_{1-4}-alkoxy;

R^b er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: halo, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-haloalkyl, C_{1-10}-haloalkoxy, $-O(CH_2)_sO(C_{1-6}$-alkyl), $-CONH(CH_2)_{6-20}H$, $-(CH_2)_m(C_{3-6}$-cycloalkyl), $-(CH_2)_m(C_{4-6}$-cycloalkenyl), $-O(CH_2)_m(C_{3-6}$-cycloalkyl), phenoxy, benzoxy, morpholinyl, 2-C_{1-4}-alkoxy-pyridin-5-yl, pyrimidin-5-yl, pyrazin-2-yl og -O-pyrimidinyl; og

R^c er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: C_{3-6}-cycloalkyl substitueret med 0-2 R^d, $-(CH_2)_m$-(phenyl substitueret med 0-3 R^d), og en heteroaryl udvalgt fra: oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, og pyrazinyl; hvor heteroarylen er substitueret med 0-2 R^d.

7. Forbindelse ifølge et hvilket som helst af kravene 1-6, hvor:

R^2 uafhængigt er udvalgt fra gruppen bestående af: CF_3 og Me;

R^3 uafhængigt er udvalgt fra gruppen bestående af: H og F;

R^4 uafhængigt er udvalgt fra gruppen bestående af: H og F;

R^6 uafhængigt er udvalgt fra gruppen bestående af: NH_2, -CONHMe, OPh, -CONH(cyclopropyl), -CONH(cyclobutyl), -CONH(cyclopentyl), -CONH(cyclohexyl), -CONHPh, -CONH(4-F-Ph), -CONH(2-Cl-Ph), -CONH(4-Cl-Ph), -CONH(4-Me-Ph), -CONH(4-OH-Ph), -CONH(3-OMe-Ph), -CONH(4-OMe-Ph), -CONH(4-CF_3-Ph), -CONH(4-OCF_3-Ph), -CONH(1-Me-pyrazol-3-yl), -CONH(4-(1*H*-tetrazol-2-yl)-Ph), -CONH(4-(2*H*-tetrazol-5-yl)-Ph), -CONH(3-F-4-Me-Ph), -CONH(3-F-4-OMe-Ph), -CONH$(CH_2)_2$Ph, -CONH(5-OMe-pyrid-2-yl), -CONH(6-OMe-pyrid-3-yl), -CONH(5-OMe-pyrazin-2-yl), -CONH(6-OMe-pyridazin-3-yl), -NHCO$(CH_2)SO_2$Me, -NHCOPh, -NHCO(2-Me-Ph), -NHCO(3-Me-Ph), -NHCO(4-Me-Ph), -NHCO(2-Cl-Ph), -NHCO(3-Cl-Ph), -NHCO(2-Cl-4-F-Ph), -NHCO(2-Cl-5-F-Ph), -NHCO(isoxazol-5-yl), -NHCO(3-Me-isoxazol-5-yl), -NHCO(4-Me-isoxazol-5-yl), -NHCO(3-OMe-isoxazol-5-yl), -NHCO(3-Br-isoxazol-5-yl), -NHCO(3-(2-Cl-Ph)-isoxazol-5-yl), -NHCO(3-(3-F-Ph)-isoxazol-5-yl), -NHCO(3-OBn-isoxazol-5-yl), 1*H*-imidazol-1-yl, -NHCO(5-Me-1,3,4-oxadiazol-2-yl), -NHCO(1-Me-1,2,3-triazol-4-yl), -NHCO(6-OMe-pyrid-3-yl), -NHCO(6-Cl-pyridazin-3-yl), 5-CF_3-1,3,4-oxadiazol-2-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl og 2*H*-tetrazol-5-yl;

R^{11} og R^{15} uafhængigt er udvalgt fra gruppen bestående af: H, Me, F og Cl;

R^{12} uafhængigt er udvalgt fra gruppen bestående af: H, F, Cl, Me og OMe;

R^{13} uafhængigt er udvalgt fra gruppen bestående af: H, F, Cl, Br, Me, OMe, OEt, CH_2OMe, CF_3, CH_2CF_3, $OCHF_2$, OCF_3, CN, $N(Me)_2$, cyclopropyl og cyclopropylmethyl;

alternativt kombineres R^{12} og R^{13}, sammen med de carbonatomer, hvortil de er bundet, for at danne en 5- til 6-leddet carbocyklisk ring eller en 5- til 6-leddet mættet heterocyklisk ring, der omfatter: carbonatomer og 1-2 oxygenatomer;

R^{14} er H;

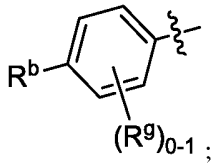
R^b er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: n-pentyl, methoxy, n-butoxy, i-butoxy, i-pentoxy, $-O(CH_2)_{1-6}CF_3$, $-O(CH_2)_{1-4}CF_2CF_3$, $-CONH(CH_2)_{6-20}H$, cyclopropyl,

cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, -O(CH$_2$)$_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl og -O-pyrimidin-2-yl; og

R^g er F.

8. Forbindelse ifølge krav 4 eller krav 5, hvor:

R^1 er



;

R^2 uafhængigt er udvalgt fra CF_3 og CH_3;

R^6 uafhængigt er udvalgt fra: R^c, -CONHR^c, -NHCOR^c, og -NHCOCH$_2$SO$_2$(C$_{1-4}$-alkyl);

R^b uafhængigt er udvalgt fra: -O(CH$_2$)$_{1-6}$CF$_3$, -O(CH$_2$)$_{1-4}$CF$_2$CF$_3$, -CONH(CH$_2$)$_{6-20}$H, cyclopent-1-en-1-yl, cyclohex-1-en-1-yl, -O(CH$_2$)$_2$(cyclopentyl), phenoxy, benzoxy, pyrimidin-5-yl, pyrazin-2-yl og -O-pyrimidin-2-yl;

R^c er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: -(CH$_2$)$_m$-(phenyl substitueret med 0-3 R^d), og en heteroaryl udvalgt fra: oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, oxadiazolyl, triazolyl, tetrazolyl, pyridyl, og pyrazinyl; hvor heteroarylen er substitueret med 0-2 R^d; og

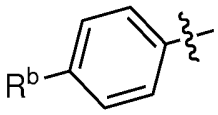
R^d er, ved hver forekomst, uafhængigt udvalgt fra gruppen bestående af: halo, OH, CN, C$_{1-4}$-alkyl, C$_{1-4}$-alkoxy, C$_{1-4}$-haloalkyl, C$_{1-4}$-haloalkoxy, tetrazolyl og OBn.

9. Forbindelse ifølge et hvilket som helst af kravene 1-6 eller 8, hvor:

R^{13} uafhængigt er udvalgt fra gruppen bestående af: H, halo, C$_{1-4}$-alkyl substitueret med 0-1 C$_{1-4}$-alkoxy, C$_{1-4}$-alkoxy, C$_{1-4}$-haloalkyl, C$_{1-4}$-haloalkoxy, CN eller C$_{3-4}$-cycloalkyl.

10. Forbindelse ifølge et hvilket som helst af kravene 1-5, 8 eller 9, hvor:

R^1 uafhængigt er



.

11. Forbindelse ifølge et hvilket som helst af kravene 1-10, hvor:

R^b uafhængigt er udvalgt fra: -O(CH$_2$)$_{1-6}$CF$_3$, og -O(CH$_2$)$_{1-4}$CF$_2$CF$_3$.

12. Forbindelse ifølge et hvilket som helst af kravene 1-5, hvor:

R^6 uafhængigt er 5-leddet nitrogenheteroaryl.

13. Forbindelse ifølge et hvilket som helst af kravene 1-12, hvor:

R^6 uafhængigt er: 1*H*-imidazol-1-yl, 1*H*-tetrazol-1-yl, 1*H*-tetrazol-3-yl eller 2*H*-tetrazol-5-yl.

14. Forbindelse ifølge krav 1, hvor forbindelsen er udvalgt fra:

3-(1*H*-tetrazol-5-yl)-4-p-tolyl-6-(4-(4,4,4-trifluorbutoxy)phenyl)-6-(trifluormethyl)-5,6-dihydropyridin-2(1*H*)-on,

(*S*)-(3-(1*H*-tetrazol-5-yl)-)-4-p-tolyl-6-(4-(4,4,4-trifluorbutoxy)phenyl)-6-(trifluormethyl)-5,6-dihydropyridin-2(1*H*)-on,

(*R*)-3-(1*H*-tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-on,

N-(4-methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-carboxamid,

(*R*)-*N*-(4-methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-carboxamid,

(*S*)-*N*-(4-methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-carboxamid,

(*S*)-3-(2*H*-tetrazol-5-yl)-4-*p*-tolyl-6-(4-(6,6,6-trifluorohexyloxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-on,

3-(2-ethyl-2*H*-tetrazol-5-yl)-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-on;

4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-3-(5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl)-5,6-dihydropyridin-2(1*H*)-on;

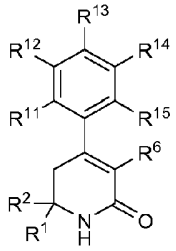
6-methyl-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-*N*-(4-(trifluoromethoxy)-phenyl)-1,2,5,6-tetrahydropyridin-3-carboxamid;

3-(2*H*-tetrazol-5-yl)-4-*p*-tolyl-6-(trifluoromethyl)-6-(1-(5,5,5-trifluoropentyl)-1*H*-pyrazol-4-yl)-5,6-dihydropyridin-2(1*H*)-on,

3-nitro-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-on;

N-(4-methoxyphenyl)-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)piperidin-3-carboxamid;

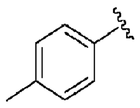
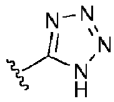
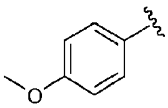
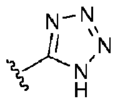
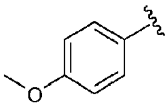
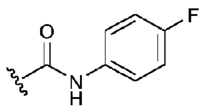
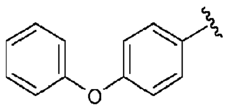
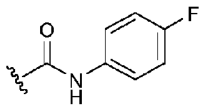
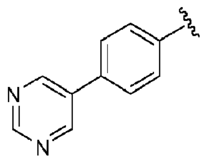
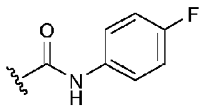
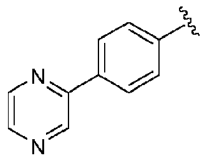
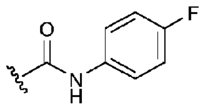
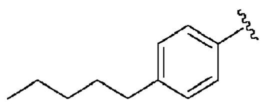
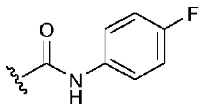
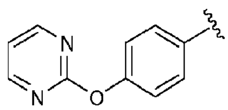
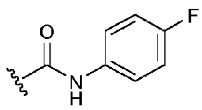
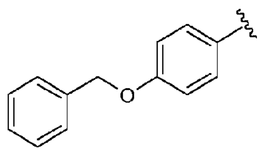
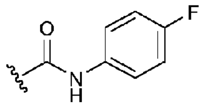
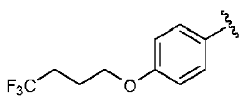
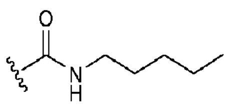
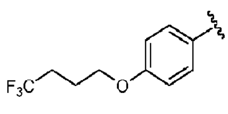
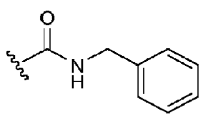
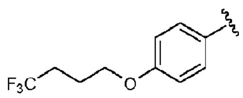
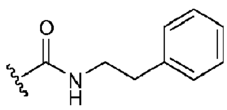
forbindelser af formlen (IIa)

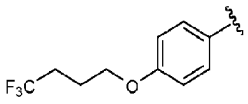
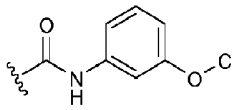
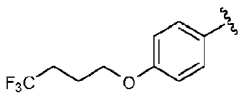
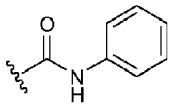
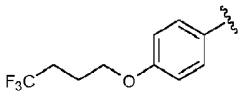
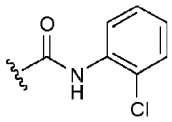
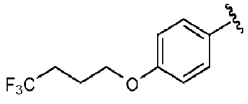
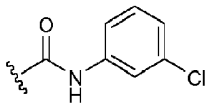
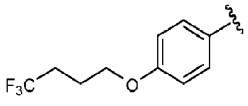
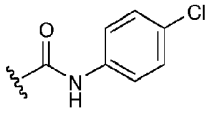
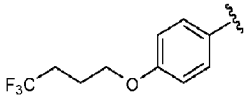
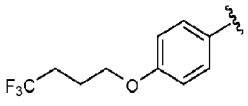
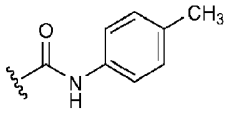
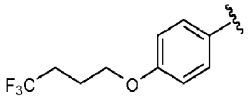
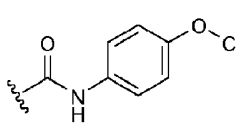
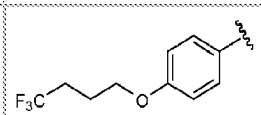
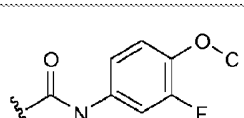
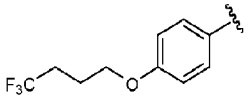
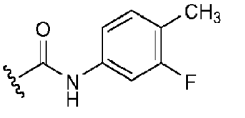
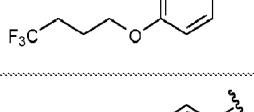
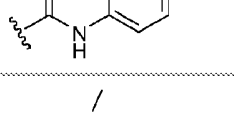
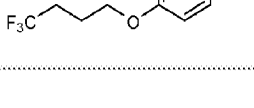
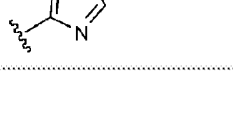


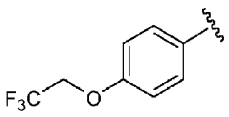
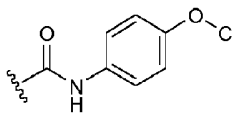
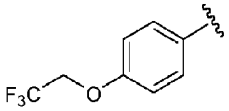
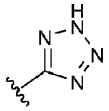
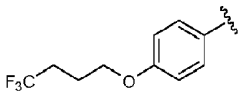
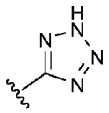
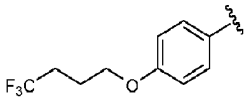
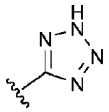
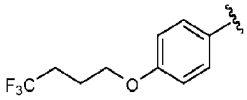
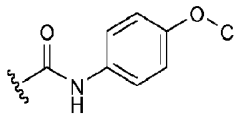
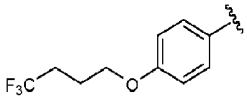
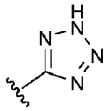
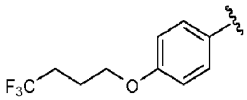
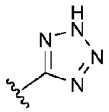
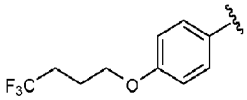
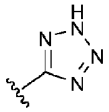
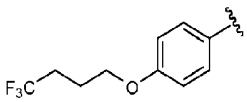
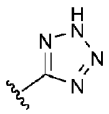
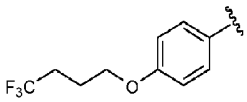
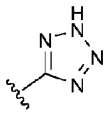
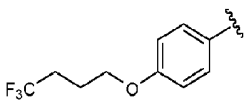
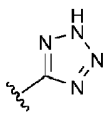
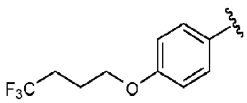
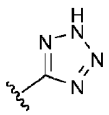
(IIa)

hvor R^1, R^2 og R^6 er substituenterne, vist i nedestående tabel, og

hvor R^{11} til R^{15} er hydrogen, medmindre andetsteds nævnt i nedestående tabel:

	R^1	R^2	R^6	R^{11}-R^{15}
Rac		CH_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$

Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$_R{}^{13} = CH_3$
Rac		CF_3	H	$_R{}^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$_R{}^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac S-isomeer		CF_3		$R^{13} = CH_3$

Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = CH_3$
Rac		CF_3		$R^{13} = OCH_2CH_3$
Rac		CF_3		$R^{13} = OCHF_2$
S-isomeer		CF_3		$R^{13} = CH_3$
S-isomeer		CF_3		$R^{11} = F$ $R^{13} = OCH_3$
Rac		CF_3		$R^{12} = CH_3$
Rac		CF_3		All H
Rac		CF_3		$R^{13} = CF_3$
Rac		CF_3		$R^{12} = Cl$
Rac		CF_3		$R^{12} = OCH_3$
Rac		CF_3		$R^{13} = Cl$

N^5-(4-methoxyphenyl)-2-methyl-6-oxo-4-*p*-tolyl-N^2-(4,4,4-trifluorobutyl)-1,2,3,6-tetrahydropyridin-2,5-dicarboxamid;

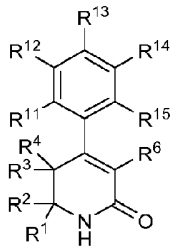
N-(4-cyanophenyl)-5,5-difluoro-2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-carboxamid;

(*S*)-3-amino-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-on;

(*S*)-2-methyl-*N*-(2-oxo-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-1,2,5,6-tetrahydropyridin-3-yl)benzamid;

(*S*)-3-phenoxy-4-*p*-tolyl-6-(4-(4,4,4-trifluorobutoxy)phenyl)-6-(trifluoromethyl)-5,6-dihydropyridin-2(1*H*)-on; og

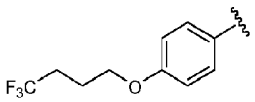
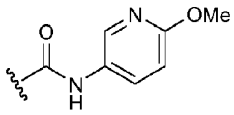
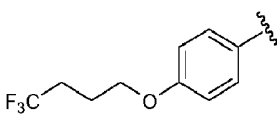
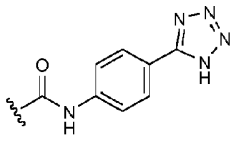
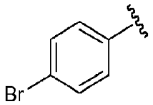
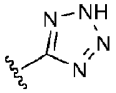
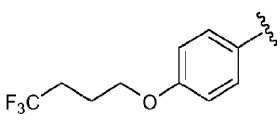
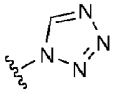
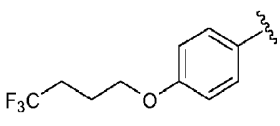
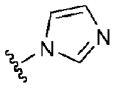
forbindelser af formel (II)

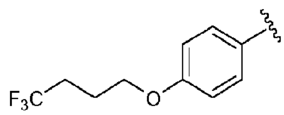
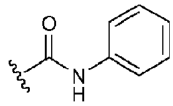
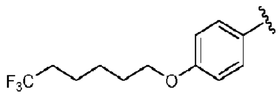
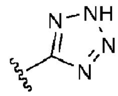
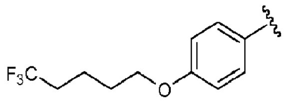
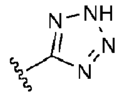
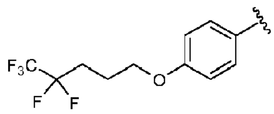
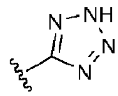
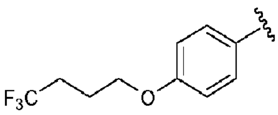
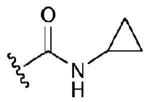
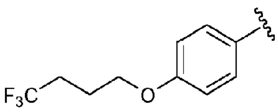
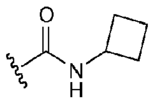
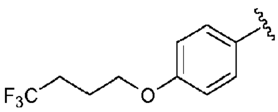
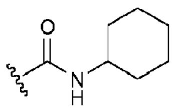
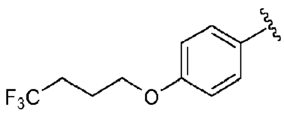
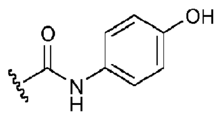
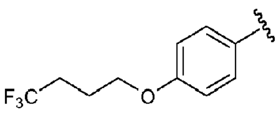
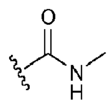
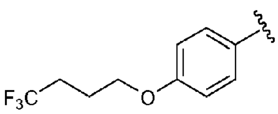
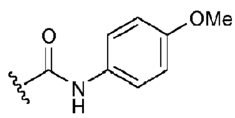
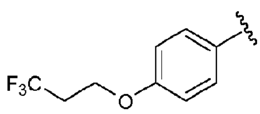
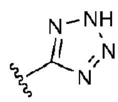
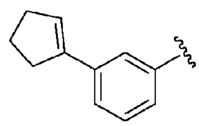
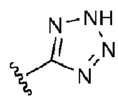


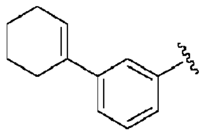
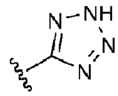
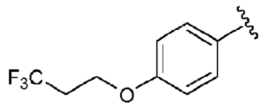
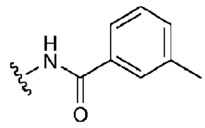
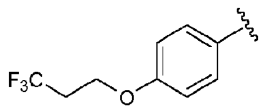
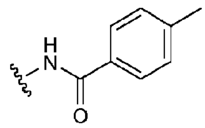
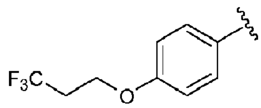
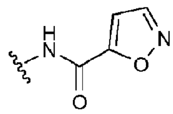
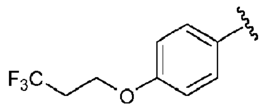
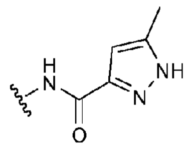
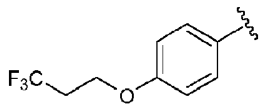
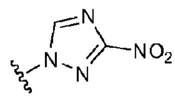
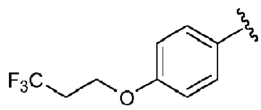
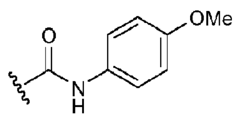
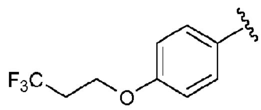
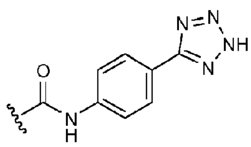
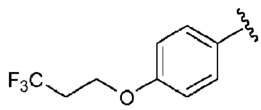
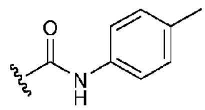
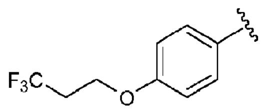
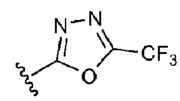
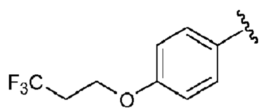
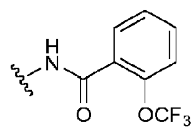
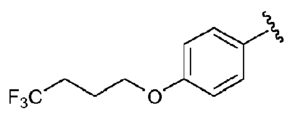
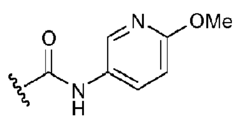
(II)

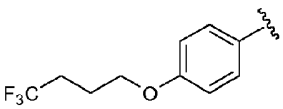
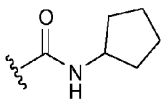
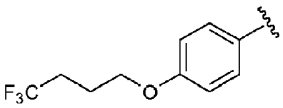
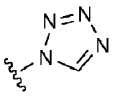
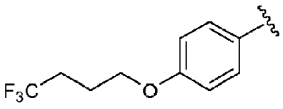
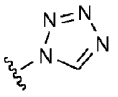
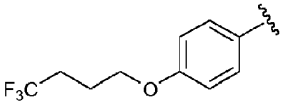
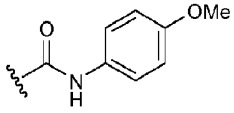
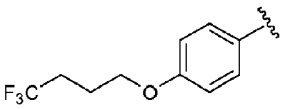
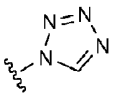
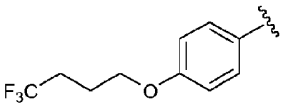
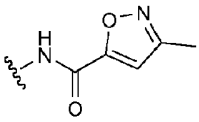
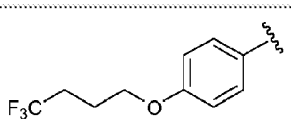
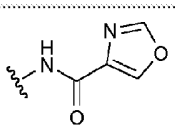
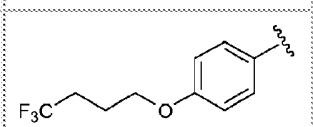
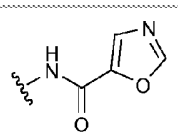
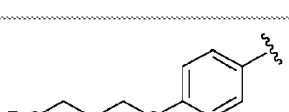
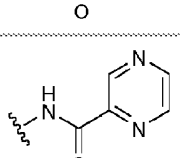
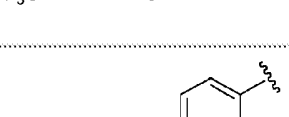
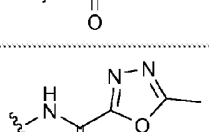
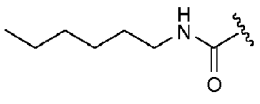
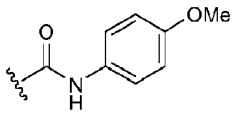
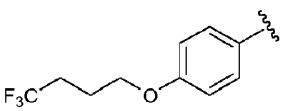
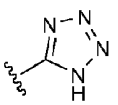
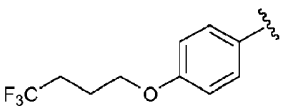
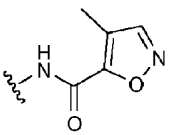
hvor R^1, R^2, R^3, R^4 og R^6 er substituenterne vist i nedestående tabel, og

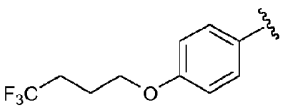
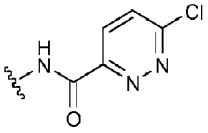
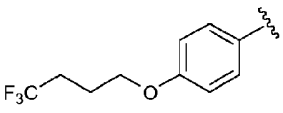
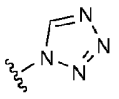
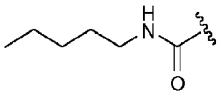
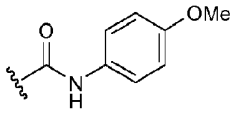
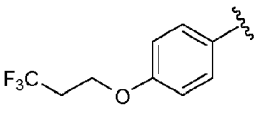
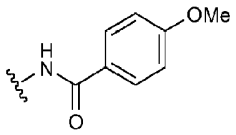
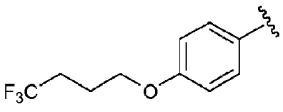
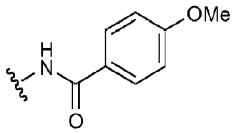
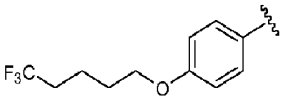
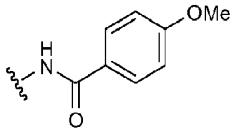
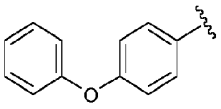
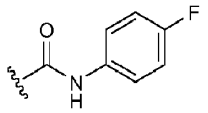
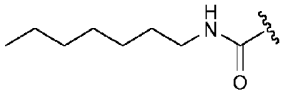
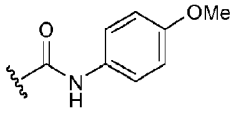
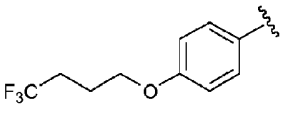
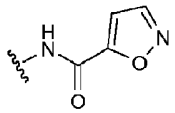
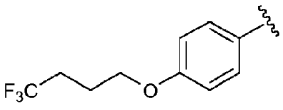
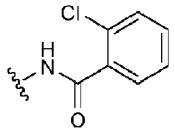
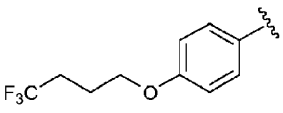
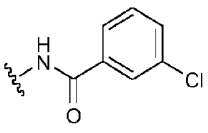
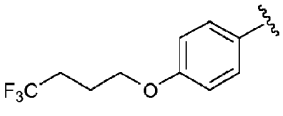
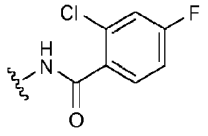
hvor R^1 til R^{15} er hydrogen, medmindre andetsteds nævnt i nedestående tabel:

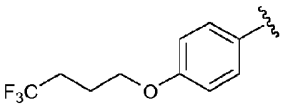
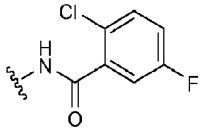
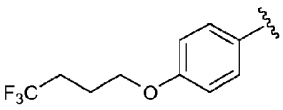
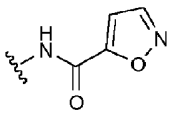
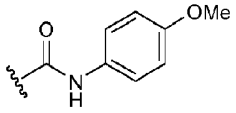
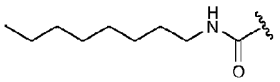
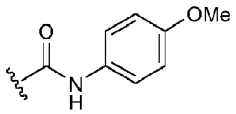
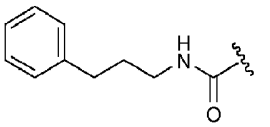
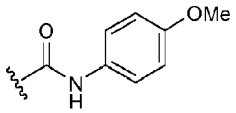
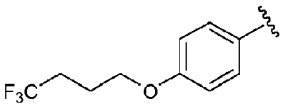
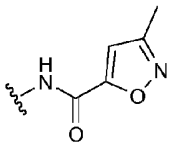
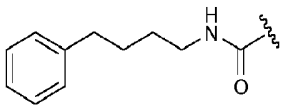
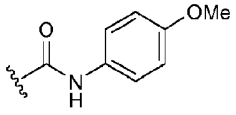
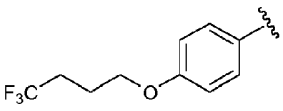
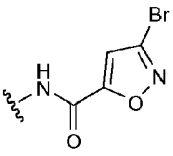
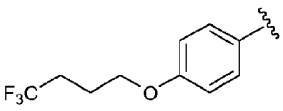
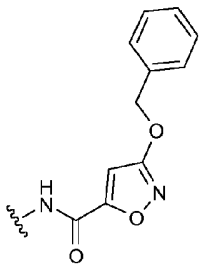
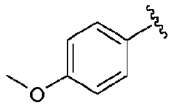
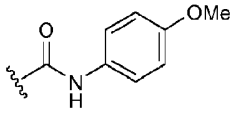
	R^1	R^2	R^3 = R^4	R^6	R^{11}-R^{15}
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$

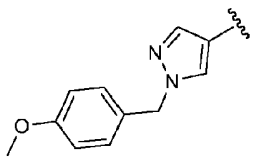
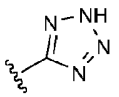
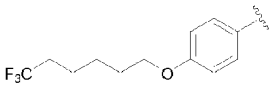
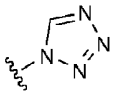
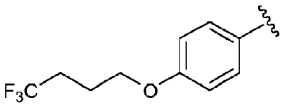
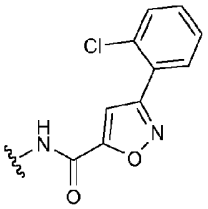
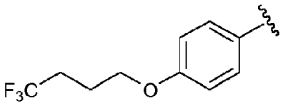
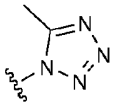
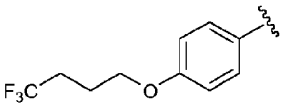
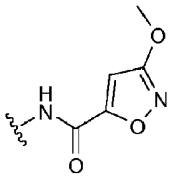
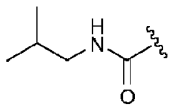
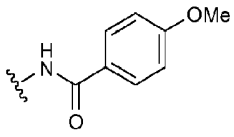
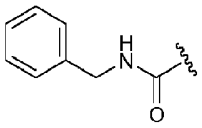
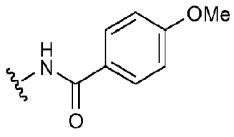
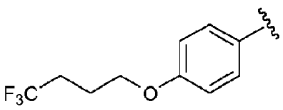
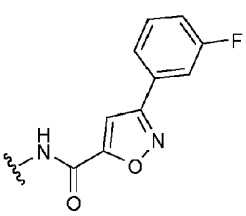
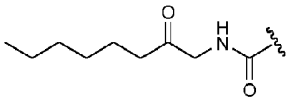
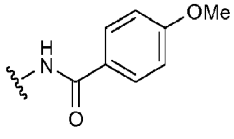
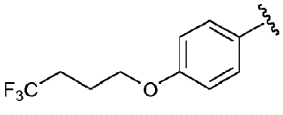
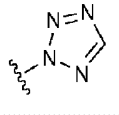
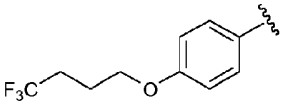
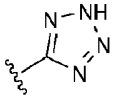
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$

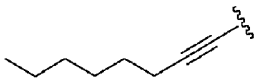
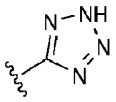
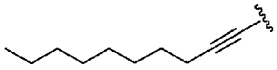
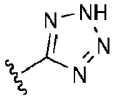
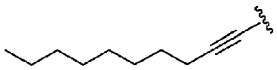
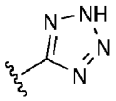
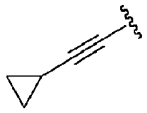
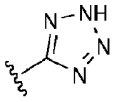
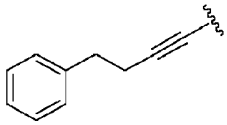
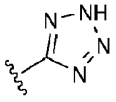
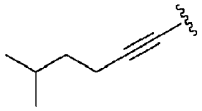
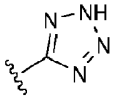
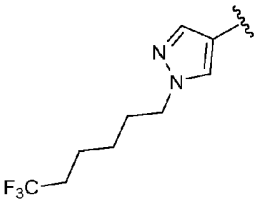
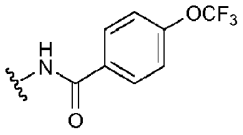
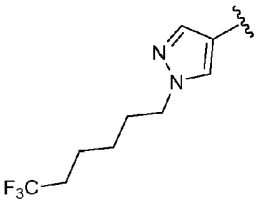
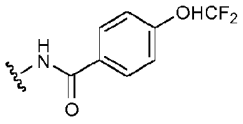
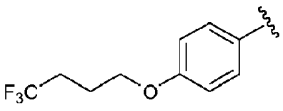
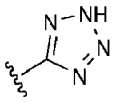
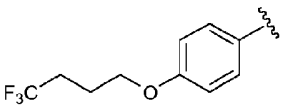
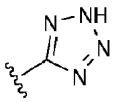
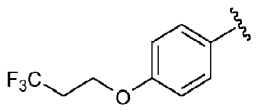
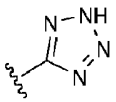
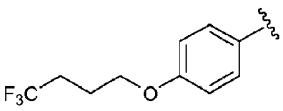
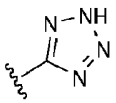
Rac		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$

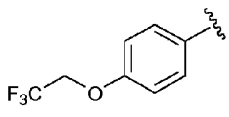
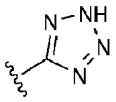
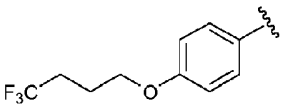
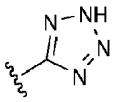
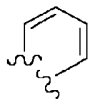
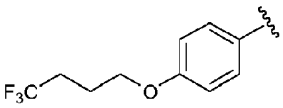
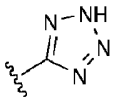
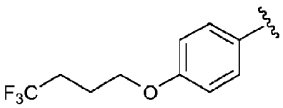
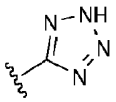
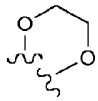
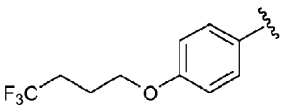
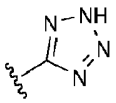
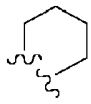
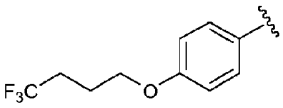
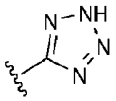
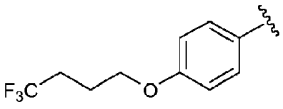
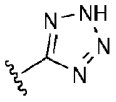
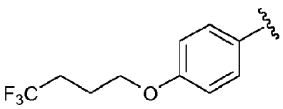
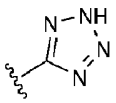
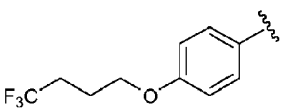
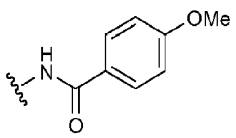
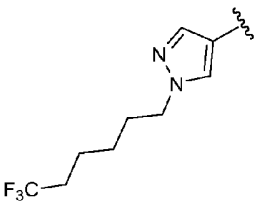
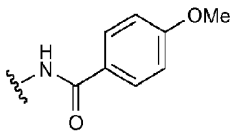
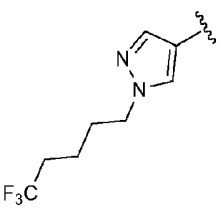
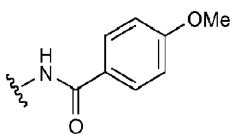
Rac		CF_3	F		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{11} = F$ $R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{11} = CH_3$ $R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCHF_2$
S-isomer		CF_3	F		$R^{13} = C^{H}_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CH_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{11} = CH_3$ $R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$

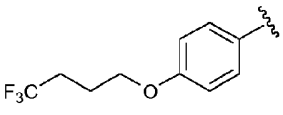
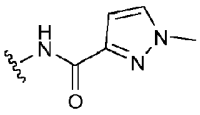
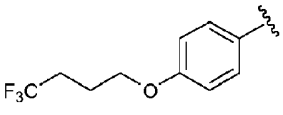
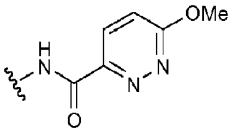
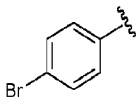
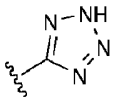
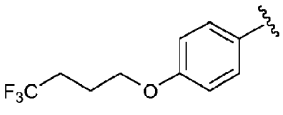
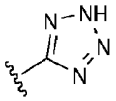
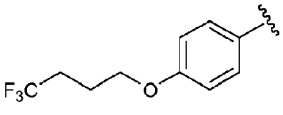
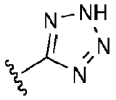
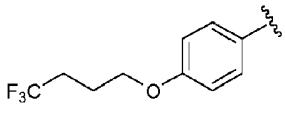
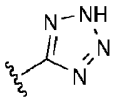
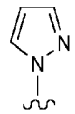
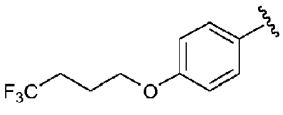
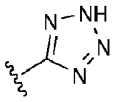
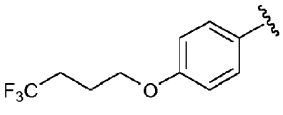
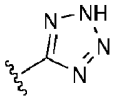
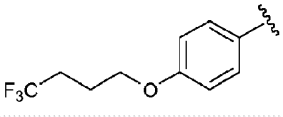
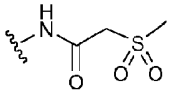
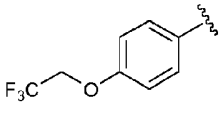
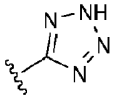
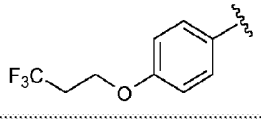
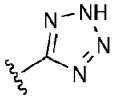
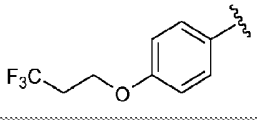
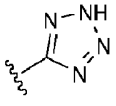
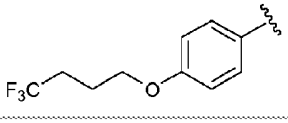
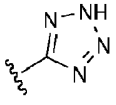
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$
Rac		CH_3	H		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CH_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OHCF_2$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$

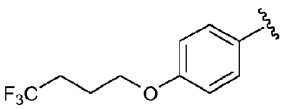
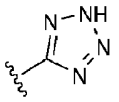
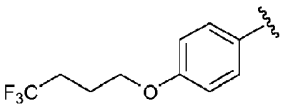
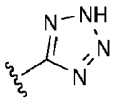
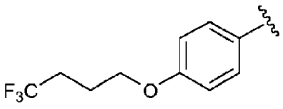
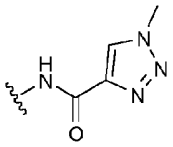
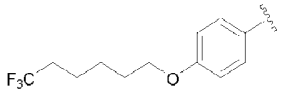
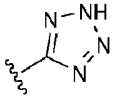
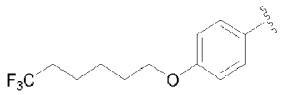
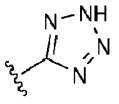
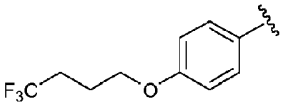
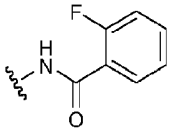
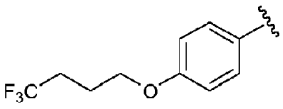
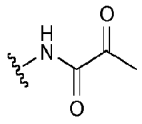
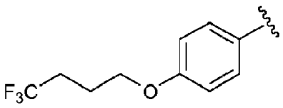
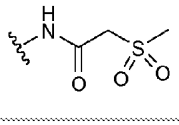
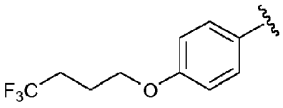
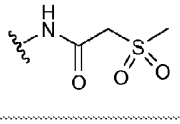
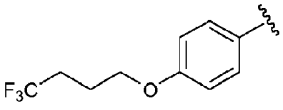
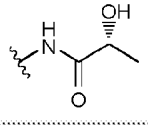
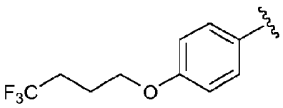
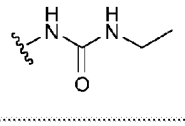
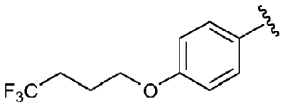
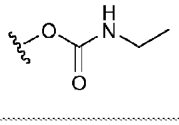
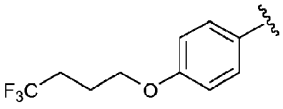
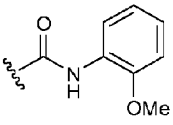
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$
Rac		CH_3	H		$R^{13} = CH_3$
Rac		CH_3	H		$R^{13} = CH_3$
Rac		CH_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$
Rac		CH_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	F		$R^{13} = CH_3$

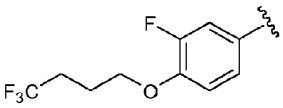
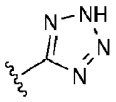
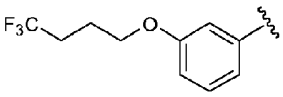
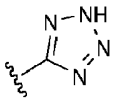
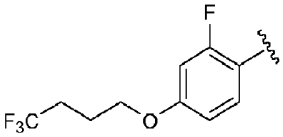
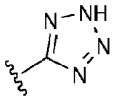
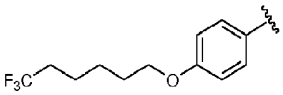
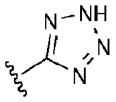
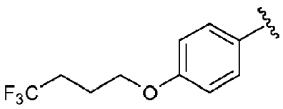
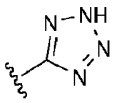
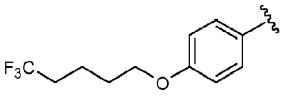
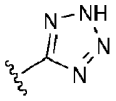
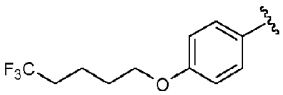
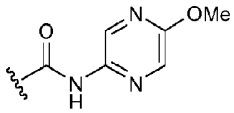
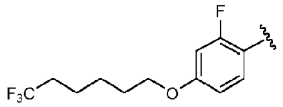
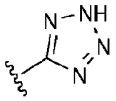
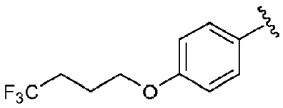
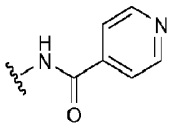
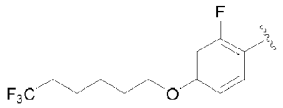
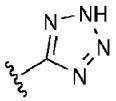
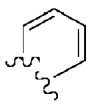
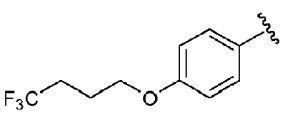
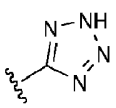
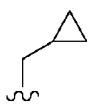
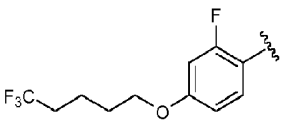
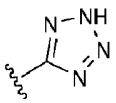
Rac		CF_3	H		$R^{13} = CH_3$
Rac S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CH_3	H		$R^{13} = CH_3$
Rac		CH_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CH_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$

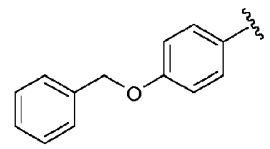
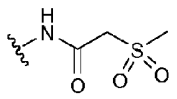
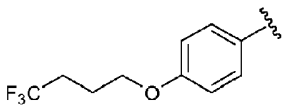
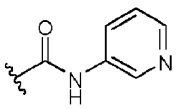
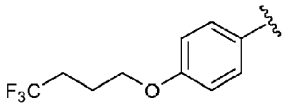
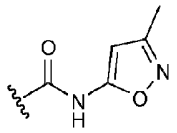
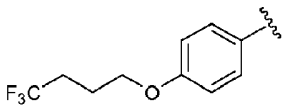
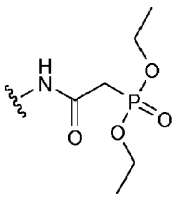
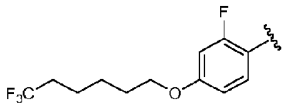
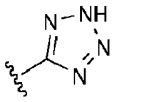
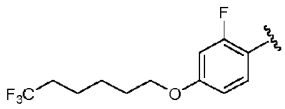
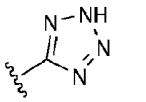
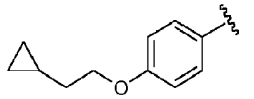
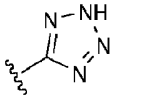
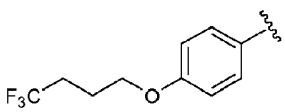
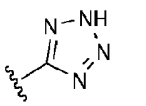
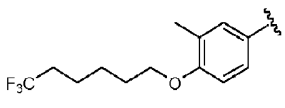
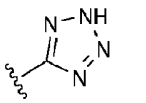
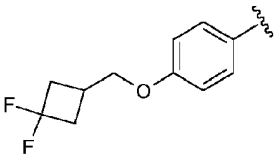
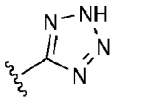
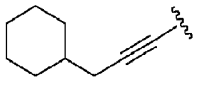
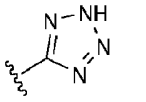
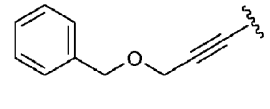
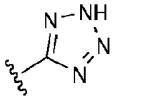
Rac		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
R-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_2OCH_3$
S-isomer		CF_3	H		R^{12} = F R^{13} = OCH_2CH_3
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCHF_2$

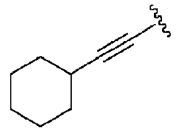
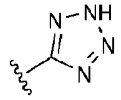
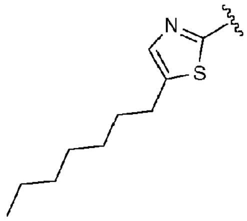
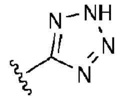
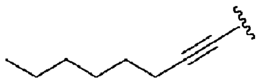
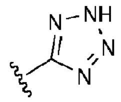
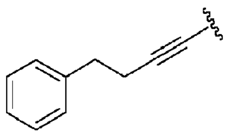
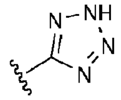
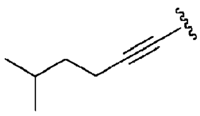
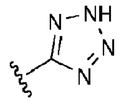
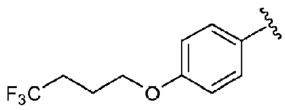
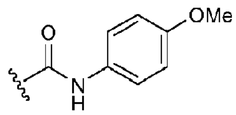
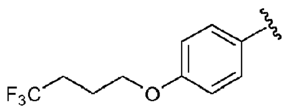
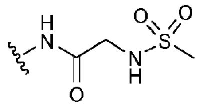
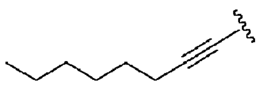
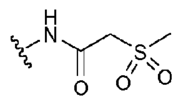
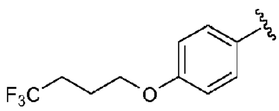
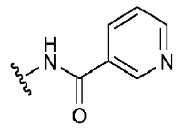
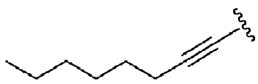
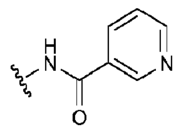
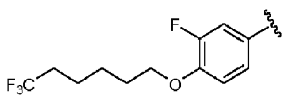
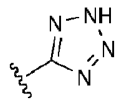
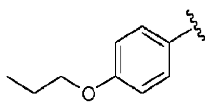
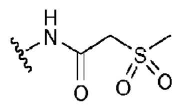
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		R^{12} R^{13} = 
S-isomer		CF_3	H		R^{13} = OCH_2CH_3
S-isomer		CF_3	H		R^{12} R^{13} = 
S-isomer		CF_3	H		R^{12} R^{13} = 
S-isomer		CF_3	H		R^{12} R^{13} = 
S-isomer		CF_3	H		R^{11} R^{12} =  R^{13} = OCH_3
S-isomer		CHF_2	H		$R^{13} = CH_3$
R-isomer		H	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$

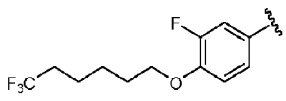
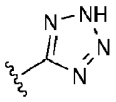
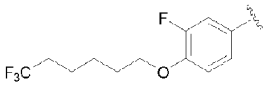
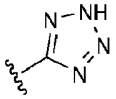
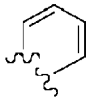
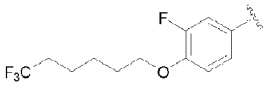
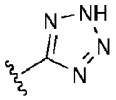
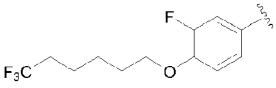
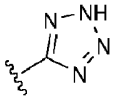
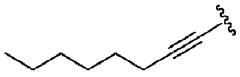
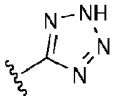
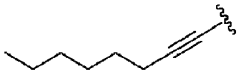
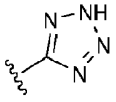
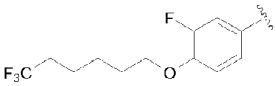
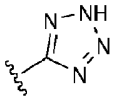
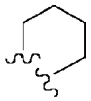
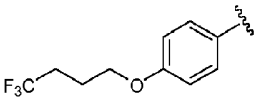
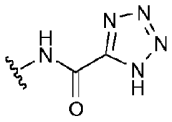
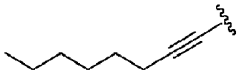
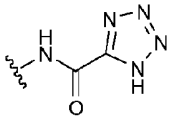
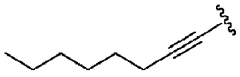
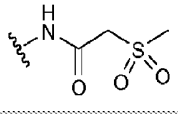
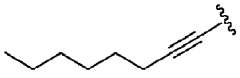
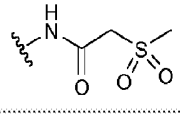
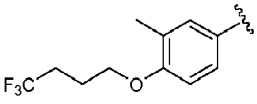
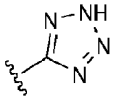
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = Br$
S-isomer		CF_3	H		$R^{13} =$ 
S-isomer		CF_3	H		$R^{13} =$ 
S-isomer		CF_3	H		R^{12} $R^{13} =$ 
S-isomer		CF_3	H		$R^{13} =$ 
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{13} = OCF_3$
S-isomer		CF_3	H		$R^{13} = OCF_3$

S-isomer		CF_3	H		$R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{13} = OCHCF_2$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{13} = OCHCF_2$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCHCF_2$
S-isomer		CF_3	H		$R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCHCF_2$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$

S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
R-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_2CF_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCHF_2$
S-isomer		CF_3	H		$R^{13} = OCHF_2$
S-isomer		CF_3	H		R^{12} R^{13} = 
S-isomer		CF_3	H		R^{13} = 
S-isomer		CF_3	H		$R^{13} = CH_3$

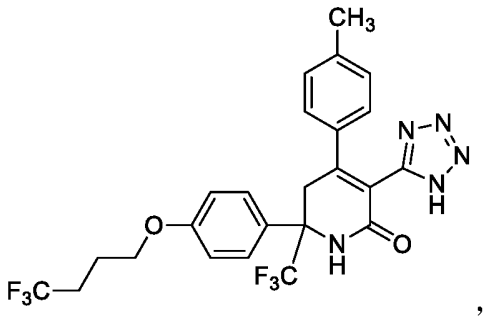
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCHF_2$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCH_2CH_3$
S-isomer		CF_3	H		$R^{13} = CH_2CF_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{11} = F$ $R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$

S-isomer		CF_3	H		$R^{13} = CH_3$
Rac		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{13} = OCH_3$
S-isomer		CF_3	H		$R^{11} = F$ $R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCHF_2$
S-isomer		CF_3	H		$R^{13} = CH_3$

S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		R^{12} R^{13} = 
S-isomer		CF_3	H		$R^{13} = OCH_2CH_3$
S-isomer		CF_3	H		$R^{13} = CH_2CF_3$
S-isomer		CF_3	H		$R^{13} = OCHF_2$
S-isomer		CF_3	H		$R^{13} = OCH_2CH_3$
S-isomer		CF_3	H		R^{12} R^{13} = 
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = CH_3$
S-isomer		CF_3	H		$R^{13} = OCH_2CH_3$
S-isomer		CF_3	H		$R^{13} = OCHF_2$
S-isomer		CF_3	H		$R^{13} = CH_3$

eller en stereoisomer, en tautomer, et farmaceutisk acceptabelt salt eller et solvat deraf.

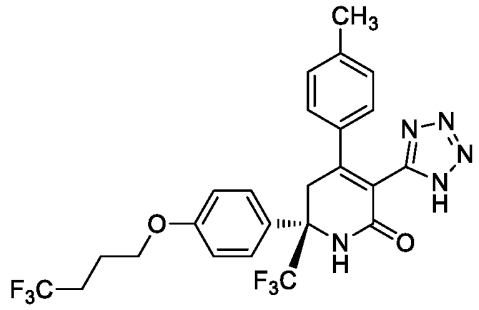
15. Forbindelse ifølge krav 1, hvor forbindelsen har følgende formel:



,

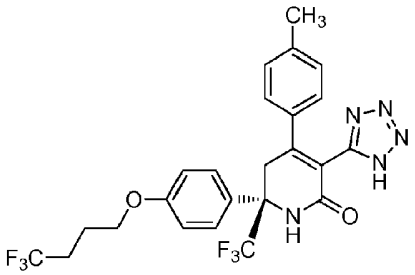
eller en stereoisomer, en tautomer eller et farmaceutisk acceptabelt salt deraf.

16. Forbindelse ifølge krav 15, hvor forbindelsen har følgende formel:



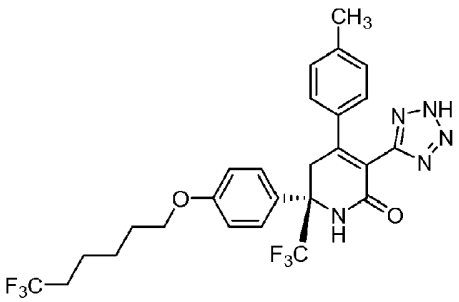
eller en tautomer, eller et farmaceutisk acceptabelt salt deraf.

17. Forbindelse ifølge krav 15, hvor forbindelsen er:



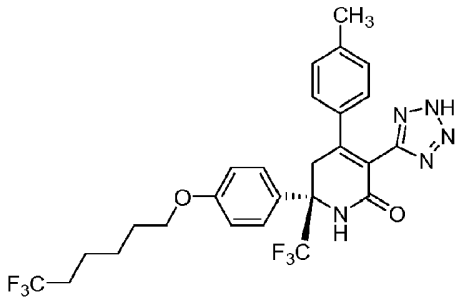
18. Farmaceutisk acceptabelt salt med forbindelsen ifølge krav 15 eller krav 16.

19. Forbindelse ifølge krav 1, hvor forbindelsen har følgende formel:



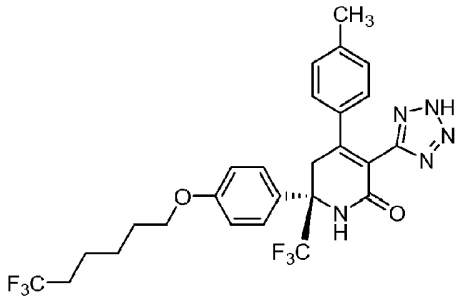
eller en stereoisomer, en tautomer, eller et farmaceutisk acceptabelt salt deraf.

20. Forbindelse ifølge krav 19, hvor forbindelsen har følgende formel:

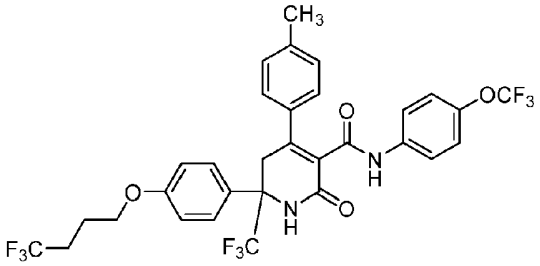


eller en tautomer eller et farmaceutisk acceptabelt salt deraf.

21. Forbindelse ifølge krav 19, hvor forbindelsen er:

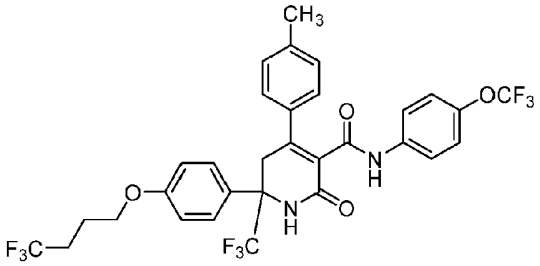


22. Forbindelse ifølge krav 1, hvor forbindelsen har følgende formel:



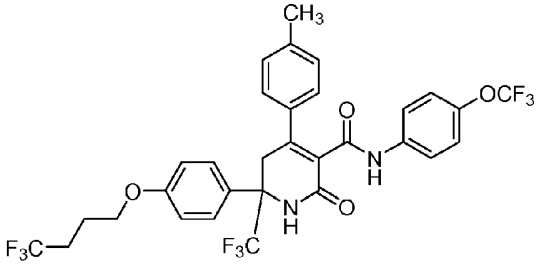
eller en stereoisomer, en tautomer eller et farmaceutisk acceptabelt salt deraf.

23. Forbindelse ifølge krav 22, hvor forbindelsen har følgende formel:

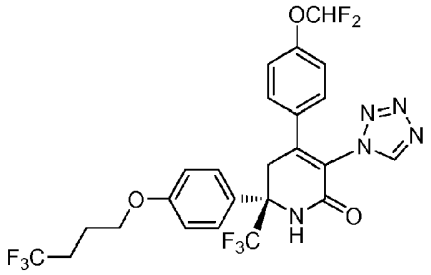


eller en tautomer eller et farmaceutisk acceptabelt salt deraf.

24. Forbindelse ifølge krav 22, hvor forbindelsen er:

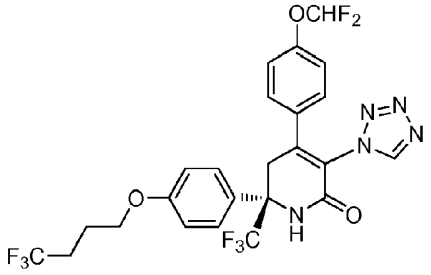


25. Forbindelse ifølge krav 1, hvor forbindelsen har følgende formel:



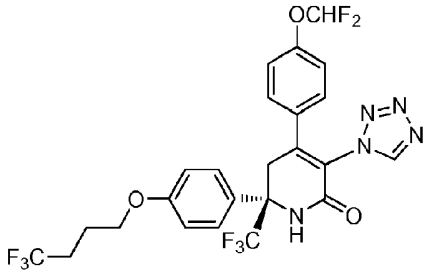
eller en stereoisomer, en tautomer eller et farmaceutisk acceptabelt salt deraf.

26. Forbindelse ifølge krav 25, hvor forbindelsen har følgende formel:

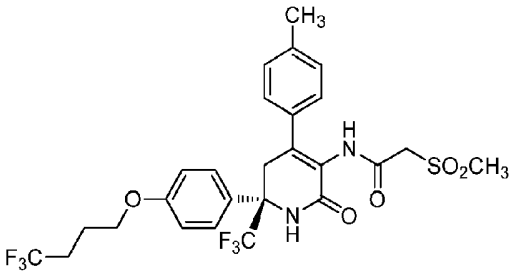


eller en tautomer eller et farmaceutisk acceptabelt salt deraf.

27. Forbindelse ifølge krav 25, hvor forbindelsen er:

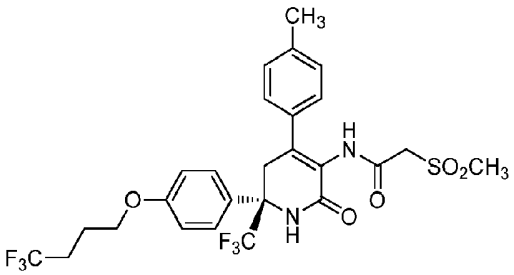


28. Forbindelse ifølge krav 1, hvor forbindelsen har følgende formel:



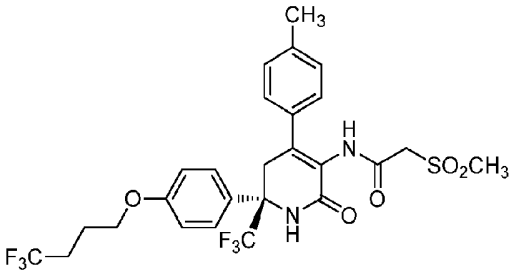
eller en stereoisomer, en tautomer eller et farmaceutisk acceptabelt salt deraf.

29. Forbindelse ifølge krav 28, hvor forbindelsen har følgende formel:



eller en tautomer eller et farmaceutisk acceptabelt salt deraf.

30. Forbindelse ifølge krav 28, hvor forbindelsen er:



31. Farmaceutisk sammensætning, der omfatter en farmaceutisk acceptabel bærer og en forbindelse ifølge et hvilket som helst af kravene 1 til 30, eller en stereoisomer, en tautomer, eller et farmaceutisk acceptabelt salt deraf, og eventuelt en eller flere yderligere terapeutiske midler.

32. Farmaceutisk sammensætning ifølge krav 31, der endvidere omfatter ét eller flere andre egnede terapeutiske midler, der er udvalgt fra: antidiabetiske midler, antihyperglykæmiske midler, antihyperinsulinæmiske midler, antiretinopatiske midler, anti-neuropatiske midler, antinefropatiske midler, antiatherosklerotiske midler, antiiskæmiske midler, antihypertensive midler, antiobesitetsmidler, antidyslipidæmiske midler, antihyperlipidæmiske midler, antihypertriglyceridæmiske midler, antihyperkolesterolemiske midler, antirestenotiske midler, lipidsænkende midler, anorektiske midler og appetitsænkende midler.

33. Farmaceutisk sammensætning ifølge krav 31, der endvidere omfatter ét eller flere andre egnede terapeutiske midler, der er udvalgt fra: en dipeptidyl peptidase-IV-inhibitor, en natrium-glukose transporter-2-inhibitor og en 11b-HSD-1-inhibitor.

34. Forbindelse ifølge et hvilket som helst af kravene 1-30, eller en stereoisomer, en tautomer, et farmaceutisk acceptabelt salt eller et solvat deraf, eller en sammensætning ifølge et hvilket som helst af kravene 18-20, til anvendelse i terapi, eventuelt simultant, separat eller sekventielt med ét eller flere yderligere terapeutiske midler.

35. Forbindelse ifølge et hvilket som helst af kravene 1 til 30, eller en stereoisomer, en tautomer, et farmaceutisk acceptabelt salt eller et solvat deraf, eller en sammensætning ifølge et hvilket som helst af kravene 18-20, til anvendelse i forebyggelse, modulering eller behandling af diabetes, hyperglycæmi, nedsat glucosetolerance, graviditetsdiabetes, insulinresistance, hyperinsulinæmi, nonalkoholisk fedtleversygdom (NAFLD) herunder nonalkoholisk steatohepatitis (NASH), retinopati, neuropati, nefropati, forsinket sårheling, atherosklerose og følgesygdomme, anormal hjertefunktion, myokardieiskæmi, apopleksi, metabolisk syndrom, hypertension, obesitet, dyslipidæmi, dyslipidæmi, hyperlipidæmi,

hypertriglyceridæmi, hypercholesterolæmi, lavt højdensitetslipoprotein (HDL), høj lavdensitetslipoprotein (LDL), ikke-iskæmisk hjertesygdom, lipidsygdomme og glaukom, eventuelt til anvendelse simultant, separat eller sekventielt med et eller flere yderligere terapeutiske midler.